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Therapeutic Review
Nonsteroidal Anti-inflammatory Drugs

Overview/Summary[1-3]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide to treat common pain and inflammatory conditions. It is estimated that more than 17,000,000 Americans use NSAIDs on a daily basis.[1] NSAIDs have been prescribed for decades and a number are available generically and/or over-the-counter (i.e., ibuprofen, ketoprofen and naproxen).[1] The NSAIDs are approved for the treatment of a variety of pain and inflammatory conditions including the treatment of: acute pain, ankylosing spondylitis, osteoarthritis, primary dysmenorrhea and rheumatoid arthritis.[1-3] In recent years newer agents have been developed in topical (Voltaren Gel®), and transdermal formulations (Flector®).[1-3]

NSAIDs inhibit cyclooxygenase (COX), (prostaglandin synthase), impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The COX enzyme can be subdivided into related isoforms, COX-1 and COX-2. The anti-inflammatory properties of NSAIDs are associated with the inhibition of COX-2, which is expressed during states of inflammation. COX-1 is expressed in most tissues and regulates normal cellular processes including: gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function.

The inhibition of COX-1 is thought to be associated with the adverse event profile of NSAIDs, including an increased risk of gastroduodenal erosions, bleeding, development of colon cancer and bronchoconstriction.[1] The adverse events associated with NSAID therapy can be severe and have resulted in a black box warning being assigned by the Food and Drug Administration (FDA). The warning advises patients that NSAIDs may be associated with an increased risk of serious cardiovascular events, stroke and gastrointestinal adverse events.[1-3] Additionally, ketorolac (Toradol®), a potent NSAID, is also contraindicated in renal impairment, patients at risk of bleeding (i.e. before surgery), and during labor, delivery, breast-feeding and coadministration with other NSAIDs.[1-4] Due to these risks, ketorolac should only be administered for acute pain (≤5 days).[1-4]

Clinical trials have demonstrated NSAIDs to be more efficacious compared to placebo in the treatment of pain and inflammatory conditions. Although there are many head to head trials comparing various NSAIDs, there is no single agent that has been continuously found to be more efficacious or safe than the others.[3] Although the efficacy of NSAIDs appears to be similar at equipotent doses, there is a wide variability of response between individual patients.[1] Therefore, it is important to frequently assess patients for efficacy and toxicity when administering NSAIDs.

Medications

Table 1. Medications Included Within Class Review†

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Diclofenac epolamine (Flector®)	Nonsteroidal anti-inflammatory drugs (NSAIDs)	-
Diclofenac potassium (Cataflam®)	NSAIDs	✔
Diclofenac sodium (Voltaren®, Voltaren Gel®, Voltaren XR®)	NSAIDs	✔ (tablets)

Generic Name (Trade name)	Medication Class	Generic Availability
Etodolac (Lodine®, Lodine XL®)	NSAIDs	✔
Fenoprofen calcium (Nalfon®)	NSAIDs	✔
Flurbiprofen (Ansaid®)	NSAIDs	✔
Ibuprofen (Motrin®)*	NSAIDs	✔
Indomethacin (Indocin®, Indocin SR®)	NSAIDs	✔
Ketoprofen (Orudis®, Oruvail®)*	NSAIDs	✔
Ketorolac tromethamine (Toradol®)	NSAIDs	✔
Meclofenamate (Meclomen®)	NSAIDs	✔
Mefenamic acid (Ponstel®)	NSAIDs	-
Meloxicam (Mobic®)	NSAIDs	✔
Nambumetone (Relafen®)	NSAIDs	✔
Naproxen and naproxen sodium (Anaprox®, Anaprox DS®, EC-Naprosyn®, Naprelan®, Naprosyn®)*	NSAIDs	✔
Oxaprozin (Daypro®, Daypro ALTA®)	NSAIDs	✔
Piroxicam (Feldene®)	NSAIDs	✔
Sulindac (Clinoril®)	NSAIDs	✔
Tolmetin sodium (Tolectin®)	NSAIDs	✔
Combination Products		
Diclofenac sodium/misoprostol (Arthrotec®)	NSAIDs/prostaglandin analogs	-

*Available as an over the counter formulation in different strengths.
† Diflunisal is not included in the review.

Indications

Table 2. Food and Drug Administration Approved Indications[2-23]

Generic Name	Relief of Mild to Moderate Pain	Relief of Signs and Symptoms of Osteoarthritis	Relief of Signs and Symptoms of Rheumatoid Arthritis	Relief of Signs and Symptoms of Juvenile Rheumatoid Arthritis	Acute or Long Term Use for the Treatment of Ankylosing Spondylitis	Treatment of Primary Dysmenorrhea	Treatment of Acute Gouty Arthritis	Treatment of Painful Shoulder (Bursitis or Tendonitis)	Short Term Management of Moderately Severe, Acute Pain Following Surgical Procedures
Single Entity Products									
Diclofenac epolamine	✔*								
Diclofenac potassium	✔	✔	✔			✔			
Diclofenac sodium†		✔	✔		✔				
Etodolac	✔	✔	✔						
Fenoprofen calcium	✔								
Flurbiprofen		✔	✔						
Ibuprofen‡	✔	✔	✔			✔			
Indomethacin		✔	✔		✔		✔§	✔	
Ketoprofen‡	✔	✔	✔			✔			
Ketorolac tromethamine									✔
Meclofenamate	✔	✔	✔			✔			
Mefenamic acid	✔					✔‖			
Meloxicam		✔	✔	✔					
Nambumetone		✔	✔						
Naproxen/ naproxen sodium‡	✔	✔	✔	✔	✔	✔	✔	✔	
Oxaprozin		✔	✔						
Piroxicam		✔	✔						
Sulindac	✔	✔	✔		✔		✔	✔	
Tolmetin sodium		✔	✔	✔					
Combination Products									
Diclofenac sodium/ misoprostol		✔¶	✔¶						

*Indicated for the treatment of acute pain associated with minor sprains and contusions.
†Extended-release diclofenac sodium is not indicated for the treatment of ankylosing spondylitis. Diclofenac gel 1% (Voltaren®) is indicated for osteoarthritis only and only of the joints amenable to topical treatment, such as the knees and the hands.
‡Over the counter product is indicated for the treatment of fever in children.
§Extended-release indomethacin is not indicated for the treatment of acute gouty arthritis.
‖ Mefenamic acid is also indicated for the treatment of idiopathic heavy menstrual blood loss.
¶ Diclofenac sodium/misoprostol is indicated in the treatment osteoarthritis or rheumatoid arthritis in patients at high risk of developing nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers and their complications.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used off-label in pain and inflammatory conditions such as migraine and the symptomatic treatment of sunburn. It is important to note that many NSAIDs are used off-label for indications that other NSAIDs are indicated for. For example, diclofenac sodium, indomethacin, naproxen and sulindac are Food and Drug Administration (FDA) approved for the treatment of ankylosing spondylitis. Etodolac and flurbiprofen are not indicated for the treatment of ankylosing spondylitis; however they have been used to treat this condition.[2]

Pharmacokinetics

Table 3. Pharmacokinetics[2-23]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products					
Diclofenac epolamine	Not reported	Renal, glucuronidation, sulfation and biliary excretion	Renal (not reported)	Not reported	12
Diclofenac potassium	55	Renal, glucuronidation, sulfation and biliary excretion	Renal (65); biliary (35)	4'-hydroxy-diclofenac	1.9
Diclofenac sodium	55 (not reported for topical dosage form)	Renal, glucuronidation, sulfation and biliary excretion	Renal (65); biliary (35) (renal, for topical dosage form % not reported)	4'-hydroxy-diclofenac	2.3 (12 for topical dosage form)
Etodolac	100 (immediate-release); >80 (extended-release)	Liver, hydroxylation and glucuronidation	Renal as parent drug and metabolites (72) and fecal (18)	Not reported	6.4 (immediate-release); 8.4 (extended-release)
Fenoprofen calcium	Not reported	Liver, glucuronidation	Not reported	Not reported	3
Flurbiprofen	96	Liver, CYP2C9	Renal (70)	4′-hydroxy-flurbiprofen, 3′,4′-dihydroxy-flurbiprofen, 3′-hydroxy-4′-methoxy-flurbiprofen	7.5
Ibuprofen	Not reported	Liver, glucurondation	Renal (not reported)	Not reported	1.8-2
Indomethacin	100 (not reported for rectal suppositories)	Liver, glucuronidation	Biliary excretion and fecal (% not reported)	Not reported	4.5
Ketoprofen	90	Liver, glucuronidation	Renal (80)	None	2-4 (ketoprofen immediate-release);

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
					5.4 (ketoprofen extended-release)
Ketorolac tromethamine	100	Liver, hydroxylation and conjugation	Renal (92); fecal (6)	Not reported	5-6
Meclofenamate	100	Liver, hydroxylation	Renal (70); fecal (30)	3' hydroxy methyl meflofenamic acid and 6 other unspecified metabolites	15.3
Mefenamic acid	Not reported	Liver, CYP2C9 and glucuronidation	Renal (52); fecal (20)	3 hydroxy methyl meflofenamic acid and 6 other unspecified metabolites	2-4
Meloxicam	89	Liver, CYP2C9 and 3A4	As metabolites in equal parts renal and fecal (% not reported)	None	15-20
Nabumetone	Not reported	Liver, conjugation	Renal (80); fecal (9)	6MNA and other unspecified metabolites	24
Naproxen and naproxen sodium	95	Liver	Renal (95)	6-0-desmethyl naproxen	12-17
Oxaprozin	95	Liver, microsomal oxidation and glucuronic acid conjugation	Renal (65); fecal (35)	Unspecified phenolic metabolites	21-25
Piroxicam	Not reported	Liver, hydroxylation and conjugation	Renal and fecal (% not reported)	None	50
Sulindac	Not reported	Oxidation and reduction	Renal (50); fecal (25)	Sulindac sulfide	7.8
Tolmetin sodium	Not reported	Oxidation and conjugation	Primarily renal	Not reported	6-7
Combination Products					
Diclofenac sodium/ misoprostol	50 (diclofenac); not reported, (misoprostol)	Liver	renal (65); bile(35) (diclofenac); renal (70) (misoprostol)	4'-hydroxy-diclofenac	2 hours (diclo-fenac); 30 minutes (miso-prostol)

Clinical Trials

There have been a vast number of clinical trials conducted evaluating the efficacy and safety of the nonsteroidal anti-inflammatory drugs (NSAIDs). However the majority of literature supporting the use of these agents was either published decades ago or are lacking in statistical significance and detail.

The efficacy of diclofenac epolamine 1.3% patch in the treatment of minor strains, sprains and contusions has been established in trials summarized in the products package insert in addition to, two published studies.[5,24-25] Per the package insert diclofenac epolamine has been found to be efficacious in two of four studies performed in patients with minor strains, sprains and contusions.[5] In the two trials demonstrating efficacy, diclofenac epolamine provided greater pain relief than placebo. Published studies in patients experiencing a sport-related sprain, strain, or contusion found that patients assigned to the diclofenac epolamine patch group exhibited significant improvement in pain scores and functioning compared to placebo. No differences in adverse events between the treatment groups were noted in these trials.[24-25]

The efficacy and safety of diclofenac 1% gel has been evaluated in patients with osteoarthritis of the hands and knees.[26-29] These randomized, double-blind, placebo-controlled trials compared diclofenac gel to placebo in adult patients. The available data tends to favor diclofenac gel in treating both hand and knee osteoarthritis. [26-29] The trials also assessed adverse events as a secondary endpoint and observed the most commonly reported adverse events to be headaches, arthralgias, application site dermatitis, back pain, and gastrointestinal events; occurring more often in the diclofenac gel group. Overall the adverse events were mild-moderate in nature. There are currently no published studies comparing diclofenac 1% gel to any oral formulation of diclofenac for the treatment of osteoarthritis.

The safety and efficacy of mefenamic acid has been evaluated in low back pain, primary dysmenorrhea and in heavy menstrual flow.[30-33] In a meta-analysis by Lethaby et al, menstrual blood loss was significantly lower in the mefenamic acid group compared to placebo. This meta-analysis contained two trials comparing mefenamic acid to naproxen and found no significant difference in measurement of blood loss between the two agents.[30] Additionally, while there was no difference in adverse events in one trial, there was a smaller risk of gastrointestinal adverse events with mefenamic acid compared to naproxen in the second trial.[30] Roefls et al compared NSAIDs (including mefenamic acid) to each other and to placebo for the treatment of low back pain.[31] Compared to placebo NSAIDs were associated with a greater reduction in pain from baseline in sciatic and nonsciatic or mixed back pain (acute and chronic). There was no difference between individual NSAIDs with respect to efficacy and adverse events.[31]

The efficacy and safety of the fixed dose combination diclofenac sodium/misoprostol has been established in the treatment of osteoarthritis and rheumatoid arthritis. Studies have shown that diclofenac sodium/misoprostol has comparable efficacy to diclofenac alone and is associated with a lower rate gastric and duodenal ulcers.[34-37] McKenna evaluated the efficacy of diclofenac sodium/misoprostol in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in comparison to diclofenac alone or other NSAIDs (ibuprofen, indomethacin, naproxen and piroxicam).[34] The results demonstrate that diclofenac sodium/misoprostol is at least as efficacious as other NSAIDs and is associated with fewer gastroduodenal ulcers than diclofenac alone. In addition, Melo Gomes et al[35] and Agrawal et al[36] observed that diclofenac sodium/misoprostol has a lower rate of occurrence of gastric/duodenal ulcers in comparison to traditional NSAIDs while Pincus et al[37] observed more gastrointestinal distress and nonserious gastrointestinal adverse events with diclofenac sodium/misoprostol than with acetaminophen.

Although there is limited data on the use of certain NSAIDs in children, they have been studied for the treatment of juvenile rheumatoid arthritis, pediatric fever and pediatric migraine.[38-40] The trials indicate that no one NSAID is consistently more efficacious than the others and that NSAIDs are generally more effective than placebo. NSAIDs have been studied extensively in pain and inflammatory conditions including lateral elbow pain, low back pain, osteoarthritis and primary dysmenorrhea.[31-33,41-43] Studies comparing the various NSAIDs have demonstrated that these agents are generally more efficacious than placebo. In addition, the studies have shown that no one NSAID has consistently been more efficacious when compared to the other agents in the class. The studies in Table 4 have been identified to best portray the safety and efficacy of the NSAIDs.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heavy Menstrual Bleeding				
Lethaby et al[30] (Cochrane Menstrual Disorders and Subfertility Group 2008) Mefenamic acid 500 mg TID from onset of menses for 4 to 5 days or until menstruation ceased vs naproxen 500 to 1,100 mg per day vs placebo	MA RCTs of NSAIDs in women 18 to 55 years of age with regular heavy periods and no pathological or iatrogenic causes for heavy menstrual blood loss	N=649 Duration varied in the 9 trials	Primary: Menstrual blood loss measured by the alkaline haematin method Secondary: Women's perception of relief and adverse events	Primary: In one trial, menstrual blood loss was significantly lower in the mefenamic acid group compared to the placebo group (WMD, -124 mL; 95% CI, -186 to -62). The other trial was not suitable for analysis. In two studies comparing mefenamic acid to naproxen, there were no significant differences found in the measurement of menstrual blood loss (WMD, 21.00; 95% CI, -5.85 to 47.85). Secondary: A significant difference was found in women's perception of "relief" of heavy menstrual bleeding between mefenamic acid and placebo (RR, 0.08; 95% CI, 0.03 to 0.18). In one study comparing mefenamic acid to naproxen, there were no significant differences in the total incidence of adverse events between treatment groups (RR, 0.12; 95% CI, 0.01 to 2.00). However, in a separate study the risk of gastrointestinal effects was significantly less in the mefenamic acid group when compared with naproxen (RR, 0.24; 95% CI, 0.06 to 0.87).
Juvenile Idiopathic (Rheumatoid) Arthritis				
Ruperto et al[38] Meloxicam oral suspension 0.125 mg/kg body weight QD vs meloxicam oral suspension, 0.25 mg/kg body weight QD vs	DB, DD, MC, RCT Children 2 to 16 years of age diagnosed with oligo-course or poly-course JIA receiving NSAID therapy	N=225 12 months	Primary: Response rates according to the ACR pediatric 30%, 50% and 70% improvement criteria in at least 3 of any 6 JIA core set variables†, with no more than 1 of the remaining variables worsening by >30%	Primary: Response rates according to the ACR pediatric 30 criteria improved from month 3 to month 12, as follows: from 63% (95% CI, 52% to 74%) to 77% (95% CI, 67% to 86%) in the meloxicam 0.125 mg/kg group, from 58% (95% CI, 47% to 69%) to 76% (95% CI, 66% to 85%) in the meloxicam 0.25 mg/kg group and from 64% (95% CI, 53% to 75%) to 74% (95% CI, 65% to 84%) in the naproxen group. No statistically significant differences in response rates were observed between the groups (*P*=0.6). Response rates according to the ACR pediatric 50 criteria improved from month 3 to month 12, as follows: from 52% (95% CI, 41% to 64%) to 68% (95% CI, 58% to 79%) in the meloxicam 0.125 mg/kg group, from 43% (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
naproxen oral suspension 10 mg/kg body weight BID There was a washout period of 1–7 days, depending on the serum half-life of the previous NSAID prior to starting treatment.			Secondary: JIA core set values, parent's evaluation of the child's pain on a 100-mm VAS as reported on the C-HAQ, parent's global assessment of the child's arthritis on a 100-mm VAS, the child's assessment of discomfort on a facial affective scale, the final global assessment of efficacy and tolerability by the investigator at months 3 and 12 on a verbal rating scale and adverse events	CI, 32% to 55%) to 65% (95% CI, 54% to 76%) in the meloxicam 0.25 mg/kg group and from 50% (95% CI, 39% to 61%) to 68% (95% CI, 58% to 78%) in the naproxen group. No statistically significant differences in response rates were observed between the groups difference (*P*=0.7). Response rates according to the ACR pediatric 70 criteria improved from month 3 to month 12 as follows: from 38% (95% CI, 27% to 50%) to 53% (95% CI, 42% to 65%) in the meloxicam 0.125 mg/kg group, from 26% (95% CI, 16% to 36%) to 43% (95% CI, 32% to 55%) in the meloxicam 0.25 mg/kg group and from 29% (95% CI, 19% to 40%) to 50% (95% CI, 39% to 61%). No statistically significant differences in response rates were observed between the groups difference (*P*=0.7). Average response rates per month over the whole treatment period were 57%, 55%, and 54%, respectively, in the groups receiving meloxicam 0.125 mg/kg, meloxicam 0.25 mg/kg and naproxen. Secondary: Patients in all 3 treatment groups demonstrated improvement from baseline in all 6 JIA core set variables and in all additional measures. This improvement was statistically significant for all JIA core set variables except the ESR. The investigators rated global efficacy as good or satisfactory in 88% of patients treated with meloxicam 0.125 mg/kg, in 85% of those treated with meloxicam 0.25 mg/kg, and in 87% of patients treated with naproxen. There were no differences in the frequency of adverse events or abnormal laboratory values between the 3 groups.
Lateral Elbow Pain				
Green et al[41] (Cochrane Musculoskeletal Group 2002) Topical NSAIDs (lecithin	MA RCTs of NSAIDs compared to placebo or	N=not reported 1 to 12 weeks	Primary: Pain as measured on VAS scale	Primary: Topical NSAIDs were associated with a significantly greater reduction in pain as measured by VAS scale than placebo (WMD, -1.88; 95% CI, -2.54 to -1.21).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
liposomal organo gel‡, diflam cream‡, iontophoresis of sodium diclofenac‡, iontophoresis of sodium salicylate‡, proglumetacin‡, diclofenac tissugel patch‡, diclofenac diethylamine salt‡) or oral NSAIDs (diflunisal, naproxen, diclofenac sodium) vs placebo or a second NSAID	another NSAID in patients aged ≥16 years of age with lateral elbow pain ≥3 weeks in duration	(14 trials)	Secondary: Patient satisfaction, adverse effects, strength, tenderness, range of motion and doctor's opinion's on response	Two trials assessed the effect of oral NSAIDs; however these were not able to be pooled. One trial demonstrated significant short term decrease from baseline on 100 mm VAS scale with diclofenac compared to placebo (WMD, -13.9; 95% CI, -23.21 to -4.59). However, the second trial showed no difference in median pain score after 4 weeks of naproxen compared to placebo. One trial compared two types of oral NSAIDs, demonstrating no differences between diflunisal and naproxen in improvement of symptoms (WMD, 0.24; 95% CI, 0.03 to 1.89) or pain relief (WMD, 0.10; 95% CI, 0.01 to 1.61). Secondary: Topical NSAIDs performed better in measures of patient satisfaction compared to placebo (RR, 0.39; 95% CI, 0.23 to 0.66). There was a significant difference demonstrated between groups with in adverse effects (RR, 2.26; 95% CI, 1.04 to 4.94). When considered individually, the frequency of the two reported adverse effects (foul breath and minor skin irritation) were not significantly different between the treatment and placebo groups. Topical NSAIDs and placebo did not significantly differ in the effects on strength, tenderness, range of motion or doctor's opinion regarding effect. Based on the results of one trial, there was significantly more abdominal pain (RR, 3.17; 95% CI, 1.35 to 7.41) and diarrhea (RR, 1.92; 95% CI, 1.08 to 3.14) reported by those taking oral NSAIDs.
Low Back Pain				
Roelofs et al[31] (Cochrane Back Group 2008) NSAIDs (naproxen, piroxicam, indomethacin, diclofenac, ibuprofen,	MA RCT, DB trials of NSAIDs in non-specific LBP with sciatica and without sciatica	N=11,237 Duration varied in the 65 trials	Primary: Change from baseline on 100 mm VAS scale Secondary: Adverse events and need for additional	Primary: Seven studies that reported on nonsciatic or mixed acute LBP indicated that NSAIDs had a greater change from baseline on 100 mm VAS scale compared to placebo (WMD, -8.39; 95% CI, -12.68 to -4.10). Four studies that reported on sciatica-only acute LBP indicated there was no statistical difference in change from baseline on 100 mm VAS scale between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ketoprofen, meloxicam, etodolac and mefenamic acid) vs a second NSAID vs paracetamol vs COX-2 inhibitors vs NSAIDs in combination with skeletal muscle relaxants vs non-drug treatments vs placebo	or mixed presentation		analgesia	NSAIDs and placebo (WMD, -0.16; 95% CI, 11.92 to 11.52). Four studies that reported on chronic LBP indicated that NSAIDs had a greater change from baseline on 100 mm VAS scale compared to placebo (WMD, -12.40; 95% CI, -15.53 to -9.26). Four studies found that NSAIDs are equally effective for pain relief and global improvement compared with paracetamol for acute LBP (RR, 1.23; 95% CI, 0.88 to 1.73) and one study found that NSAIDs were more effective (diflunisal vs paracetamol; *P* value not reported). Five studies compared COX-2 inhibitors with traditional NSAIDs and found no statistically significant differences for pain relief for acute LBP (WMD, -1.17; 95% CI, -4.67 to 2.33). One study found no difference between COX-2 inhibitors and NSAIDs in the relief of chronic LBP (WMD, 2.00; 95% CI, -1.92 to 5.92). Three studies compared some type of NSAID with NSAIDs plus muscle relaxants for acute LBP. In all three studies, the combination of an NSAID with a muscle relaxant was more efficacious than the NSAID alone, although there were no statistically significant differences (*P* values not reported). Secondary: In 10 of 11 studies comparing NSAIDs to placebo in acute LBP, there were significantly fewer adverse effects in the placebo group compared to the NSAID group (RR, 1.35; 95% CI, 1.09 to 1.68). In 4 of 11 studies comparing NSAIDs to placebo in acute LBP, there was significantly less additional analgesic use in the NSAID group compared to the placebo group (RR, 0.80; 95% CI, 0.71 to 0.91). In 4 studies comparing NSAIDS to placebo in chronic LBP there were significantly fewer adverse events in the placebo group compared to the NSAID group (RR, 1.24; 95% CI, 1.07 to 1.43).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Based on 33 head to head studies comparing two or more NSAIDs, there seems to be no difference in the reported number and severity of side effects for the various types of NSAIDs. NSAIDs were associated with more adverse events compared to paracetamol (RR, 1.76; 95% CI, 1.12 to 2.76) and COX-2 inhibitors (RR, 0.83; 95% CI, 0.70 to 0.99).
Osteoarthritis				
Watson et al[42] (Cochrane Musculoskeletal Group 2006) NSAID (etodolac, piroxicam, diclofenac, and tenoxicam‡) vs a second NSAID	MA DB, RCTs comparing the efficacy of two NSAIDs in the management of patients aged 16 years or older with clinically or radiologically confirmed osteoarthritis of the knee	N=not reported Duration varied between 4 and 12 weeks for the 16 trials	Primary: Withdrawal due to lack of efficacy Secondary: None reported	Primary: In nine trials with etodolac, there was no difference in withdrawal due to lack of efficacy between etodolac and diclofenac (RR, 1.03; 95% CI, 0.25 to 4.23) and between etodolac and naproxen (RR, 1.20; 95% CI, 0.32 to 4.53). In three trials, there was a trend favoring a lower withdrawal due to lack of efficacy with etodolac compared to piroxicam (RR, 0.41; 95% CI, 0.09 to 1.83) However, a lower dose of piroxicam was used in all three trials. Based on the results of one trial, there was a significantly lower withdrawal rate due to lack of efficacy with tenoxicam compared to piroxicam (RR, 3.93; 95% CI, 1.07 to 14.44). Secondary: None reported
Bjordal et al[43] Paracetamol vs oral NSAIDs (diclofenac, diflunisal, etodolac, nabumetone, naproxen, oxaprozin, tiaprofenic acid‡, valdecoxib‡, celecoxib, meloxicam, lumiracoxib‡)	MA R, PC, trials comparing patients (median age of 63.2 years) treated with specified interventions for clinically or radiologically confirmed knee	N=14,060 Duration varied in the 63 trials	Primary: Reduction in pain intensity from baseline, as measured on the WOMAC index or on a 100 mm VAS for global or walking pain within 4 weeks of treatment start Secondary: Reduction in pain	Primary: The mean baseline pain intensities on 100 mm VAS were 72.8 mm for opioid therapy, 64.3 mm for oral NSAIDs, 57.4 mm for steroid injections, 54.9 mm for paracetamol, 54.7 mm for topical NSAIDs, 53.8 mm for glucosamine sulfate and 50.7 mm for chondroitin sulfate. The maximum pain-relieving effect seen with oral NSAIDs as measured by a decrease from baseline on 100 mm VAS observed at 2.3 weeks (10.2 mm; 95% CI, 8.8 to 11.6). The values dropped slightly at 4 weeks (9.0 mm; 95% CI, 4.9 to 13.1). The maximum pain relief for topical NSAIDs as measured by a decrease from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs topical NSAIDs (diclofenac, eltenac gel‡, and ibuprofen gel‡) vs steroid injection (triamcinolone, methylprednisolone, cortivazol) vs glucosamine sulfate vs chondroitin sulfate vs opioids (codeine, oxymorphone, oxycodone, morphine sulfate, tramadol) The dosage regimens varied between the trials.	osteoarthritis lasting for a duration of at least 3 months		intensity from baseline, as measured on the WOMAC index or 100 mm VAS scale for global or walking pain at 8-12 weeks, heterogeneity of primary and secondary outcome measure and corresponding subgroup analysis	baseline on 100 mm VAS appeared after a mean of 1.6 weeks (11.6 mm; 95% CI, 7.4 to 15.7), while pain relief dropped at 4 weeks (7.0 mm; 95% CI, 5.5 to 8.6). The maximum pain relief for steroid injection efficacy as measured by a decrease from baseline on 100 mm VAS was at the first post injection evaluation at 1.5 weeks (14.5 mm; 95% CI, 9.7 to 19.2) decreasing by week 4 (6.7 mm; 95% CI, 0.4 to 13.0). There was not enough data to identify a time point for maximum pain relief with paracetamol, glucosamine and chondroitin sulfate. However, there was a 3.0 mm (95% CI, 1.4 to 4.7), a 4.7 mm (95% CI, –0.3 to 9.1) and a 3.7 mm (95% CI, 0.3 to 7.0) decrease from baseline on 100 mm VAS identified within the 4 week time frame, respectively. The pain relief associated with opioids as measured by a decrease from baseline on 100 mm VAS scale was calculated to 12.9 mm (95% CI, 8.4 to 17.4) at 2–4 weeks. However, withdrawal rates were high and intention-to-treat analyses were only presented in last value carried forward scenarios. Secondary: The efficacy as measured by decrease from baseline on 100 mm VAS of paracetamol did not change at week 12 during the follow-up period (4.0 mm; 95% CI, 1.1 to 6.9). The efficacy as measured by decrease from baseline on 100 mm VAS gradually declined at week 12 during follow-up for oral NSAIDs (9.8 mm; 95% CI, 6.9 to12.8), topical NSAIDs (7.0 mm; 95% CI, 1.0 to 13.0) and intra-articular steroid injections (5.7 mm; 95% CI, 1.4 to 10.1). For topical NSAIDs, there was a decrease from baseline on 100 mm VAS scale at 4 weeks (1 trial; 7.0 mm; 95% CI, 1.0 to 13.0) and at 12 weeks (1 trial; 6.2 mm; 95% CI, 1.0 to10.9). For intra-articular steroid injections, there were decreases from baseline on

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				100 mm VAS scale at 6 weeks (2 trials; 5.6 mm; 95% CI, 4.4 to 15.6) and after 8 to 12 weeks (4 trials; 5.5 mm; 95% CI, 0.8 to 10.2). For glucosamine sulfate, there was a decrease from baseline on 100 mm VAS scale at week 8 (3.8 mm; 95% CI, 1.4 to 9.0) and at week 12 (5.6 mm; 95% CI, 1.1 to 12.2). Based on the results of 6 trials with chondroitin sulfate, there was a larger decrease from baseline on 100 mm VAS at week 8 (7.1 mm; 95% CI, 3.3–10.8) and at week 12 (10.6 mm; 95% CI, 6 to 15.2) than was seen at the end of 4 weeks. Based on the results of 1 trial with opioids, there was a decrease from baseline on 100 mm VAS scale at 12 weeks (10.2 mm; 95% CI, 4.1 to 16.3). 49.4% of the randomized patients completed the trial. Heterogeneity in trial samples for the primary outcomes for oral NSAIDs (Q-value 58.9; *P*=0.001; decrease of 10.2 mm from baseline on VAS; 95% CI, 9.0 to 11.9) was assumed to result from patient selection bias in trials which excluded patients who did not experience a flare of symptoms after being taken off their NSAID prior to treatment allocation (non responders). Subgroup analyses showed a reduction of heterogeneity to non-significance for pain data in both subgroups (*P*≥0.3; Q-value, 13.8 and 10.8 for biased and unbiased trials, respectively). There was a significantly greater maximum decrease from baseline on VAS scale (*P*<0.001) for the subgroup of 14 trials which excluded non-responders compared to the 12 trials that included non-responders (11.8 mm; 95% CI, 10.5 to 13.1 vs 7.9 mm; 95% CI, 6.9 to 8.9). The results for secondary outcomes were consistent with these findings (*P*<0.001). Heterogeneity in trial samples for the primary outcomes topical NSAIDs (Q-value 23.2; *P*=0.002; decrease of 11.6 mm on VAS; 95% CI, 6.1 to 16.5) was assumed to be caused by inefficacy of one of the three different gels (eltenac) and use beyond 2 weeks.

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				There was no heterogeneity in outcome measures during the first 4 weeks of treatment for glucosamine sulfate, chondroitin sulfate and paracetamol (Q-values of 1.3, 1.8 and 2.3, respectively).
Novartis[26§] Diclofenac gel 4 g QID on target knee vs placebo	DB, MC, PC, PG, RCT Patient's ≥35 years of age with a history of clinical osteoarthritis of the knee for ≥6 months per ACR criteria and X-ray, able to tolerate rescue medication and had a baseline VAS score of ≥50 mm measuring POM and a baseline WOMAC score of ≥9.	N=480 12 weeks	Primary: WOMAC pain score and physical function score and global rating of disease at week 12 Secondary: Incidence of adverse events	Primary: At week 12, the mean change from baseline score for WOMAC pain measures were 5.85 for diclofenac patients and 4.68 for placebo patients (*P*=0.023). The least squares mean for the differences in change from baseline to endpoint for WOMAC was 1.3 (95% CI, 0.2 to 2.5; *P*=0.023). The WOMAC physical function score mean decline from baseline favored the diclofenac group compared to placebo group (17.5 vs 11.8, respectively; *P*=0.003). The least squares mean for the differences in change from baseline to endpoint for WOMAC physical function score was 5.7 (95% CI, 2.0 to 9.4; *P*=0.003). The global rating of disease score favored the diclofenac group vs placebo as the mean decline from baseline was 30.0 vs 22.4, respectively (*P*=0.018). The least squares mean for the differences in change from baseline to endpoint for WOMAC physical function score was 8.5 mm (95% CI, 1.5 to 15.6; *P*=0.003). Secondary: Treatment-related adverse events were 60.2% in the diclofenac group and 53.8% in the placebo group. The most common adverse events were: headache (13.8% vs 14.3%, respectively), arthralgia (13.4% vs 8.8%, respectively), and back pain (9.1% vs 6.7%, respectively). Application site dermatitis was more common in the diclofenac group (4.3% vs 1.7%, respectively), while gastrointestinal-related adverse events were similar among the groups (5.9% vs 5.0%). Four serious adverse events were observed (2 patients per group); however none were determined to be drug related.
Novartis[27§] Diclofenac gel 2 g QID on	DB, MC, PC, PG, RCT	N=385 8 weeks	Primary: Osteoarthritis pain intensity score,	Primary: At weeks 4 and 6, there were statistically significant differences between treatment groups in osteoarthritis pain intensity scores. At week 4, the mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
target hand vs placebo	Male or female patient's ≥40 years with primary osteoarthritis of the hand via ACR criteria and X-ray verification		AUSCAN and global rating of disease activity assessed at weeks 4 and 6 using 100 mm VAS Secondary: Incidence of adverse events	change from baseline was 31.1 for the diclofenac group and 23.9 for placebo (*P*=0.018). At week 6 the mean change from baseline was 33.7 for the diclofenac group and 26.7 for placebo (*P*=0.023). The difference between treatment groups in total AUSCAN scores at week 4 and 6 was also statistically significant. At week 4, the mean change from baseline was 23.5 for the diclofenac group and 16.8 for placebo (*P*=0.011); while the mean change at week 6 was 25.9 for the diclofenac group and 18.6 for placebo (*P*=0.006). The difference in treatment groups for the global rating of disease scores at week 4 were 20.8 vs 14.8, respectively; (*P*=0.06). By week 6 the mean change from baseline was 23.1 for the diclofenac group and 16.3 for placebo (*P*=0.023). The differences between treatment arms were statistically significant at week 4 for pain intensity (6.0 mm; 95% CI, 1.1 to 11.0; *P*=0.018) and AUSCAN (6.3 mm; 95% CI, 1.5 to 11.2; *P*=0.011), but not for global rating of disease activity (4.9 mm; 95% CI, -0.2 to 9.9; *P*=0.06). Secondary: The treatment group had a 52.0% rate of adverse events vs 43.9% for the placebo group. The most frequently observed events were: musculoskeletal and connective tissue disorders (13.6% vs 17.6%, respectively) nervous system disorders (13.6% vs 12.3%, respectively), and infections/infestations (12.6% vs 7.0%, respectively). Headaches were the most common adverse events reported (11.1% vs 10.2%, respectively). The overall incidence of gastrointestinal adverse events was 7.6% for diclofenac patients and 3.7% for placebo patients.
Novartis[28§] Diclofenac gel 2 g QID on target hand vs	DB, MC, PC, PG, RCT Patients ≥40 years with a diagnosis of	N=not specified 8 weeks	Primary: Osteoarthritis pain intensity score, total AUSCAN index, and global rating of disease activity assessed via	Primary: There were no differences between treatment groups in any of the 3 primary endpoints. At week 4 the mean change from baseline in osteoarthritis pain intensity scores was 22.2 for the diclofenac group and 19.5 for placebo, with a least

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	primary osteoarthritis via ACR criteria and X-ray		100 mm VAS Secondary: Incidence of adverse events	squares mean difference of 2.0 mm (95% CI, -2.1 to 6.2; *P*=0.33); the total AUSCAN scores were 16.4 mm for diclofenac patients and 13.1 mm for placebo patients, with a least squares mean difference of 2.6 mm (95% CI, -1.0 to 6.1; *P*=0.16); and the global ratings of disease score was 14.4 mm for the diclofenac patients and 13.5 mm for the placebo patients, with a least squares mean difference of 0.3 mm (95% CI, -3.6 to 4.1; *P*=0.89). Results beyond week 4 were not available. Secondary: Treatment-related adverse events were reported in 29.7% of diclofenac patients and 29.1% of placebo patients. The most common adverse event categories were: nervous system disorders (7.9% vs 11.7%, respectively), musculoskeletal and connective tissue disorders (7.9% vs 6.6%, respectively), and infections/infestations (5.4% vs 8.7%, respectively). Headaches were the most common adverse event reported (6.9% vs 9.7%, respectively). Application site dermatitis was not reported in the placebo patients, but occurred in 2.5% of diclofenac patients. Gastrointestinal adverse events were 4.0% for diclofenac patients and 5.1% for placebo patients, with the most reported event of toothaches.
Novartis[29§] Diclofenac gel 4 g QID on target knee vs placebo	DB, MC, PC, PG, RCT Patients ≥35 years of age with a history of clinical osteoarthritis of the knee for at least 6 months per ACR criteria and X-ray, able to tolerate rescue medication and	N=not specified 12 weeks	Primary: WOMAC index and physical function scores, Global rating of disease scores at week 12 Secondary: Incidence of adverse events	Primary: At week 12, the mean change from baseline score for WOMAC pain measures were 4.8 for diclofenac patients and 4.4 for placebo patients, a difference of 0.4 (95% CI, -0.3 to 1.1; *P*=0.31). The WOMAC physical function score mean decline from baseline favored the diclofenac group compared to placebo group (14.4 vs 12.8, respectively), a difference of 1.6 (95% CI, -0.7 to 3.9; *P*=0.17). The global rating of disease score favored the diclofenac group vs placebo as the mean decline from baseline was 25.1 mm vs 22.4 mm, respectively, a difference of 2.8 mm (95% CI, -1.8 to 7.4; *P*=0.23).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	had a baseline VAS score of ≥50 mm measuring POM and a baseline WOMAC score ≥9			Secondary: Treatment-related adverse events were 53.7% in the diclofenac group and 47.1% in the placebo group. The most common adverse events were: headache (16.6% vs 16.5%, respectively), arthralgia (6.9% vs 5.9%, respectively), and back pain (6.9% vs 7.5%, respectively). Nasopharyngitis was more common in the diclofenac group (6.2% vs 2.4%, respectively), while gastrointestinal-related adverse events were lower among the diclofenac group (3.1% vs 3.9%), with the most common gastrointestinal event being nausea.
Agrawal et al[36] Diclofenac sodium 75 mg/ misoprostol 200 µg BID (combination entity) vs nabumetone 1,500 mg QD vs placebo	DB, PC, PG, MC, RCT Patients with symptomatic osteoarthritis of the hip or knee with a history of endoscopically confirmed gastric, pyloric-channel or duodenal ulcer or ≥10 erosions in the stomach or duodenum	N=1,095 6 weeks	Primary: Difference in rate of endoscopically confirmed combined gastric and duodenal ulceration at final visit Secondary: Difference of endoscopically confirmed gastric ulcers and duodenal ulcers alone at final visit, rate of combined gastric and duodenal ulcers based on *H. Pylori* status	Primary: There was a significantly lower combined incidence of gastric and duodenal ulcers in the diclofenac/misoprostol group compared to the nabumetone group (4% vs 11%, respectively; *P*<0.001) at final visit. There was no significant difference in ulceration between the diclofenac/misoprostol group and the placebo group (4% vs 5%, respectively; *P*=0.525). Secondary: There was a significantly lower incidence of gastric ulceration in the diclofenac/misoprostol group compared with the nabumetone group (1% vs 9%, respectively; *P*<0.001) and the placebo group (1% vs 4%, respectively; *P*=0.044) There was no difference in incidence of duodenal ulceration between the diclofenac/misoprostol group and the nabumetone group (4% vs 3%, respectively; *P*=1.00) and the placebo group (4% vs 1%, respectively; *P*=0.154). There was no significant differences in combined gastric and duodenal ulcer rates based on *H. pylori* status across treatment groups (*P*=0.560).
Melo Gomes et al[35] Diclofenac sodium 50 mg/ misoprostol 200 µg BID (combination entity) vs	DB, MC, PG, RCT Patients with symptomatic osteoarthritis of the hip and/or knee, who	N=643 4 weeks	Primary: Incidence of gastroduodenal, gastric and duodenal ulcers on endoscopy after 4 weeks and change in severity of osteoarthritis index	Primary: There were significantly fewer gastroduodenal ulcers on endoscopy after 4 weeks in the diclofenac/misoprostol group compared to the naproxen group (*P*=0.001) and the piroxicam group (*P*<0.001). No significant difference was found between the piroxicam and naproxen groups (*P*=0.56). There were significantly fewer gastric ulcers on endoscopy after 4 weeks in the diclofenac/misoprostol group in comparison to the naproxen group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
naproxen 375 mg BID vs piroxicam 10 mg BID	required continuous NSAID drug therapy for 4 weeks		from baseline to week 4 Secondary: Change from baseline in the physician's global assessment and patient's global assessment of arthritic condition, compliance and adverse events	(*P*=0.004) and the piroxicam group (*P*=0.007). No significant difference was found between the piroxicam and naproxen groups (*P*=0.78). There were significantly fewer duodenal ulcers on endoscopy after 4 weeks in the diclofenac/misoprostol group compared to the piroxicam group (*P*=0.002).There was no difference between the naproxen group in comparison to the diclofenac/misoprostol group or the piroxicam group (*P* values not reported). There was a significantly greater decrease from baseline in the osteoarthritis severity index at week 4 in the diclofenac/misoprostol group compared to the piroxicam group (*P*=0.004).There was no significant difference between the naproxen group and the diclofenac/misoprostol group or the piroxicam group (*P* values not reported). Secondary: No treatment differences were found in the analyses of change from baseline in the physician's global assessment or patient's global assessment of arthritic condition between all treatment groups (*P*=0.78 and *P*=0.27 for overall comparisons, respectively). No significant differences between the three treatment groups in mean compliance with study medication was noted at the final visit (95% in all treatment groups; *P* value not reported). The incidences of abdominal pain and diarrhea were higher in the diclofenac/ misoprostol group than in the piroxicam group (abdominal pain: 20.8% vs 15.7%, respectively; diarrhea: 18.1% vs 5.5%, respectively; *P* values not reported) or naproxen group (abdominal pain: 20.8% vs 17.6%, respectively; diarrhea: 18.1% vs 4.8%, respectively; *P* values not reported).
Pincus et al[37] Diclofenac sodium 75 mg/ misoprostol 200 µg BID (combination entity)	DB, MC, RCT, XO Patients >40 years of age and	N=227 12 weeks	Primary: Decrease in pain as measured by WOMAC and MHDAQ during two 6 week periods	Primary: There was a significantly greater decrease in WOMAC scale rating of the most involved joint rating from baseline in the diclofenac/misoprostol group in comparison to the APAP group during the first 6 week period (12.2 from 42.5 vs 6.6 from 44.8, respectively; *P*=0.011) and the second 6 week period (12.9

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs APAP 1,000 mg QID	Kellgren/ Lawrence radiographic grade 2-4 osteoarthritis of the knee or hip and ≥30 mm pain on a 100-mm VAS		Secondary: Additional measures of pain including: SF-36 scores of pain and physical function, MDHAQ sub scores for ADL and global health, WOMAC sub scores for pain stiffness and function, investigators' assessment of patient global status and change in status and adverse events	from 40.5 vs 2.1 from 37.4, respectively; *P*<0.01). There was a significantly greater decrease in MDHAQ VAS pain scores in the diclofenac/misoprostol group in comparison to the APAP group in the first 6 week period (20.8 from 53.7 vs 13.1 from 53.3; *P*<0.01) and the second 6 week period (24.6 from 53.3 vs 0.4 from 45.3; *P*<0.01). Secondary: Additional efficacy scores including SF-36 pain and physical function scores, MDHAQ scores for basic ADL, and global health, WOMAC subscale scores for pain, stiffness, and function and investigators' estimates of patient global status and change in status over 6 weeks all favored the diclofenac/ misoprostol group in comparison to the APAP group (*P*<0.05 for all values). There was a significantly higher MDHAQ gastrointestinal distress scale score when patients took diclofenac/misoprostol than when patients took APAP across both periods (*P*=0.013). Any adverse event was reported by a significantly greater number of patients in the diclofenac/misoprostol group compared to the APAP group (54% of 195 patients vs 46% of the 205 patients, respectively; *P*<0.046). Any nonserious adverse gastrointestinal event was more common in the diclofenac/ misoprostol group in comparison to the APAP group (34% vs 24%, respectively; *P*<0.006).
Pain and Inflammation				
Zacher et al[44] Diclofenac topical preparations (treatment regimen varied)	MA DB, PC, RCTs in soft-tissue injuries, soft-tissue rheumatic disorders and osteoarthritis	N=3,000 Duration varied in the 19 trials	Primary: Pharmacokinetic and Pharmacodynamic parameters, efficacy and safety endpoints Secondary: Not reported	Primary: Topical diclofenac has good skin penetration and a localized effect based upon characteristics including a low volume of distribution, short half-life, and mild acidity. Onset of action was shown to be relatively rapid in acute pain studies, with differences in onset between topical formulations. Various topical diclofenac products were generally well tolerated, with minor

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				application site skin irritation as the primary associated side effect. Secondary: Not reported
Pediatric Migraine				
Silver et al[39] APAP vs ibuprofen vs triptans (sumatriptan, zolmitriptan, and rizatriptan) vs dihydroergotamine vs placebo	MA Blinded PC, RCTs in children and adolescents 4 to 17 years of age for the treatment of pediatric migraine	N=3,150 Duration not reported for the 11 trails	Primary: Proportion of patients with headache relief 2 hours post-treatment and the proportion of patients with complete pain relief 2 hours following treatment Secondary: Not reported	Primary: APAP was not significantly more effective than placebo in generating headache relief at 2 hours (RB, 1.46; 95% CI, 0.96 to 2.21) or complete pain relief 2 hours after treatment (RB, 1.21; 95% CI, 0.24 to 2.29). Ibuprofen was significantly more effective than placebo in providing headache relief 2 hours following treatment (RB, 1.50; 95% CI, 1.15 to 1.95) and complete pain relief after 2 hours (RB, 1.92; 95% CI, 1.28 to 2.86). Sumatriptan was significantly more effective than placebo in providing headache relief 2 hours post-treatment (RB, 1.26; 95% CI, 1.13 to 1.41) and complete pain relief 2 hours post treatment (RB, 1.56; 95% CI, 1.26 to 1.93). Zolmitriptan was less effective than placebo at producing headache relief 2 hours post-treatment (RB, 0.93; 95% CI, 0.77 to 1.13), although this result was not statistically significant. Zolmitriptan was not significantly more effective than placebo in generating complete pain relief 2 hours following treatment (RB, 1.27; 95% CI, 0.84 to 1.90). Rizatriptan was not significantly more effective in providing headache relief after 2 hours (RB, 1.05; 95% CI, 0.95 to 1.16). Rizatriptan was associated with a nearly significant proportion of patients pain free 2 hours following treatment (RB, 1.21; 95% CI, 0.99 to 1.48). Dihydroergotamine produced more headache relief 2 hours post-treatment than placebo (RB, 3.50; 95% CI, 0.91 to 13.53). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pediatric Pain and Fever				
Perrott et al[40] Ibuprofen vs APAP Al of the doses were typically 10 mg/kg in the evaluated studies.	MA Blinded, RCTs with children aged <18 years of age receiving single dose APAP or ibuprofen to treat fever or moderate to severe pain	N=1,820 Duration varied for the 17 trials however only efficacy data regarding response to first dose included in analysis	Primary: Proportion of participants showing at least 50% of maximum pain relief at 2 and 4 hours post dose, mean between-drug difference in temperature at 2, 4, and 6 hours after treatment and mean between-drug difference in temperature reduction from baseline at these time points Secondary: Risk ratio for minor harm (adverse event not leading to withdrawal from study) and major harm (withdrawal of a patient from study due to an adverse event) and risk ratio of major and minor harm compared to placebo	Primary: Ibuprofen was associated with greater pain control than APAP at 2 hours (1.14; 95% CI, 0.82 to 1.58) and 4 hours (1.11; 95% CI, 0.89 to 1.38) post dose. Ibuprofen was associated with a greater decrease in fever than APAP at 2 hours (0.19; 95% CI, 0.05 to 0.33), 4 hours (0.31; 95% CI, 0.19 to 0.44) and at 6 hours (0.33; 95% CI, 0.19 to 0.47). Secondary: The median duration of adverse events assessment was 48 hours after commencing treatment, but there was considerable variability, ranging from 4 hours to 14 days across studies. APAP was associated with a greater risk of minor harm than ibuprofen (RR, 0.96; 95% CI, 0.68 to 1.36), however because the 95% confidence interval contained values on either side of 1.00, there is no clear evidence that the drugs differed in risk of minor harm. There was no difference in the risk of major harm (RR, 1.00; 95% CI, 0.55 to 1.82). The risk ratio of ibuprofen compared to placebo was 1.17 (95% CI, 0.68 to 2.03) for minor harm and 1.51 (95% CI, 0.45 to 5.05) for major harm. The risk ratio of APAP compared to placebo was 0.79 (95% CI, 0.42 to 1.48) for minor harm and 0.90 (95% CI, 0.25 to 3.29) for major harm.
Primary Dysmenorrhea				
Marjoribanks et al[32] (Cochrane Metabolic and Endocrine Disorders Group 2003)	MA RCTs assessing the use of	N=4,066 Duration of studies	Primary: Relief of pain associated with primary dysmenorrhea	Primary: NSAIDs were significantly more effective than placebo in producing moderate to excellent pain relief and overall pain relief (OR, 7.91; 95% CI, 5.65 to 11.09) except nimesulide (OR, 3.97; 95% CI, 1.10 to 14.34).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ASA 650 mg every 4 hours vs dexketoprofen‡ 12.5-25 mg every 6 hours vs diclofenac up to 200 mg daily in divided doses, orally or by suppository vs etodolac 200-300 mg BID vs fenoprofen100-200 mg every 4 hours vs fentiazac‡ 100 mg BID twice daily vs flufenamic acid‡ 200 mg every 8 hours vs flurbiprofen 100 mg BID	NSAIDs in the treatment of primary dysmenorrhea in women aged 12 to 47	varied in the 63 trails (44 XO and 19 parallel) from 1 to 5 cycles	(outcome measures varied but included: percentage of patients experiencing moderate to excellent pain relief, overall pain relief and reduction in post treatment pain scores from baseline) Secondary: Adverse events, absence from school or work, requirement of additional medication to treat symptoms and restriction of daily activities	There was a significant reduction in post treatment pain scores in two parallel design trials including fenoprofen vs ASA (0.79 [SD 0.90] vs 1.44 [SD 1.04] respectively; *P*<0.01) and nimesulide vs mefenamic acid (6.80 [SD 0.81] vs 5.27 [SD 1.16] respectively; *P*<0.01). One XO trial demonstrated a greater percentage of efficacy in cycles with indomethacin compared to ASA (71% vs 40%; *P*<0.001). No significant difference in pain relief measures was reported in the remaining head to head parallel and XO trials (corresponding *P* values >0.05). Secondary: There was no significant difference in the incidence of: gastrointestinal adverse events such as nausea and indigestion between placebo and any individual NSAID (corresponding *P* values >0.05) and NSAIDs overall (OR, 1.70; 95% CI, 0.89 to 3.25); nervous system adverse events such as headache, drowsiness, dizziness and dryness of the mouth between placebo and any individual NSAID (corresponding *P* values >0.05) and NSAIDs overall (OR, 1.82; 95% CI, 0.76 to 4.32);and total adverse events between placebo and any individual NSAID (corresponding *P* values >0.05). There was a significantly greater incidence of an adverse event of any kind with NSAIDs overall compared to placebo (OR, 1.52; 95% CI, 1.09 to 2.12). There was no significant difference between the evaluated NSAIDs and the incidence of GI, nervous system and total adverse events (corresponding *P* values >0.05). In four parallel trials, there was significantly less absenteeism from work or school when participants were taking NSAIDs (diclofenac and naproxen) compared to placebo (for diclofenac, OR, 0.07; 95% CI, 0.01 to 0.32; for naproxen, OR, 0.23; 95% CI, 0.13 to 0.34; NSAID overall, OR, 0.20; 95% CI, 0.12 to 0.34). In one XO trial, there was significantly less absenteeism with indomethacin compared to placebo (*P* value not reported). One XO trial

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs glucametacin‡ 210 mg BID vs ibuprofen 400 mg TID, QID or six times daily vs indomethacin 25 mg tablets or 100 mg suppositories TID vs ketoprofen 25-50 mg every 6 hours, (with or without a loading dose of 25-70 mg) vs lysine clonixinate‡ 125 mg every 6 hours vs meclofenamate sodium 100 mg every 8 hours vs mefenamic acid 250 mg				comparing ibuprofen to naproxen found no significant difference in absenteeism between the two agents and a second XO trial comparing ibuprofen to flurbiprofen did not report whether its results were significant. There was no statistically significant difference in the requirement for additional analgesia between any individual NSAID and placebo except with naproxen (OR, 0.22; 95% CI, 0.13 to 0.35). However, there was a statistically significant difference which favored NSAIDs overall when compared to placebo (OR, 0.33; 95% CI, 0.23 to 0.47). One XO study found that women were significantly less likely to require additional analgesia with ibuprofen compared to placebo (*P*<0.0001). Three XO and two parallel design studies compared the requirement for additional analgesia between NSAIDs. There was no significant difference between the two compared agents in four studies (ibuprofen vs fenoprofen; ibuprofen vs piroxicam; ASA vs fenoprofen; naproxen vs piroxidine; *P* values <0.05) and the significance of the results of the final study was not reported (naproxen vs flurbiprofen; *P* value not reported). In three parallel design trials, women taking NSAIDs were significantly less likely to report restriction of daily activities than women taking placebo (for fenoprofen, OR, 0.21; 95% CI, 0.05 to 0.90; for naproxen, OR, 0.38; 95% CI, 0.19 to 0.78; NSAIDs overall, OR, 0.36; 95% CI, 0.20 to 0.64). There was no difference in the percentage of women who reported restriction of daily activities between aspirin and placebo (*P* value not reported). One XO design trial found that women were significantly less likely to report restriction of daily activities with ibuprofen than with placebo (*P*<0.001). A second XO trial found no statistically significant difference in this measure between naproxen and placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 8 hours vs naproxen or naproxen sodium 250-275 mg every 4 to 8 hours (with or without a loading dose of 500-550 mg) vs niflumic acid‡ 250 mg TID vs nimesulide‡ 50-100 mg BID vs piroxicam 20-40 mg QD, by tablet or suppository vs tolfenamic acid‡ 200 mg every 8 hours vs placebo				
De Mello et al[33] Meloxicam 7.5 QD	DB, DD, MC, PG, RCT Female	N=337 3-5 days for 3 con-	Primary: Reduction in lumbar and abdomino-pelvic pain from baseline as	Primary: There was a significant decrease in lumbar and abdomino-pelvic pain on the VAS scale from baseline to the second and third menstrual cycles in all three treatment groups (*P* values not reported). There was no difference between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs meloxicam 15 mg QD vs mefenamic acid 500 mg TID	outpatients 18 to 40 years of age with symptoms of primary dysmenorrhea during the last 3 consecutive menstrual periods	secutive menstrual cycles	measured by a VAS scale on 4 consecutive visits (baseline and during 1st, 2nd and 3rd cycle) Secondary: Patient's and investigators assessment of treatment, incidence of symptoms of dysmenorrhea (fatigue, nervousness, headache, diarrhea, dizziness, diaphoresis, and vomiting), onset of drug action, ability to work and disability to perform daily activities as measured by VAS scale and safety	responses to the two dosages of meloxicam (*P* values not reported). Significant decreases from baseline between VAS assessments taken at the second and the third menstrual cycles were observed when analyzing lumbar pain with meloxicam 7.5 mg and mefenamic acid 1,500 mg and abdomino-pelvic pain with meloxicam 15 mg (*P* values not reported). Secondary: 85% of the patients included in the trial considered the treatment result as "Good" or "Satisfactory." Investigators opinion rated the treatment results as "Good" or "Satisfactory" in 86% of the subjects. There was no difference in patterns of global assessment of efficacy, either by patient or by investigators among the three treatment groups (*P* value not significant for patient assessment comparison; *P*=0.0347 for investigator assessment comparison). The most frequently reported symptoms associated with dysmenorrhea were fatigue (87%), nervousness (85%) and headache (72%). The remaining symptoms reported included: dizziness (57%), diaphoresis (42%), vomiting (38%) and diarrhea (26%). There was a significant decrease in these symptoms at baseline and at visits 3 (second cycle) and 4 (third cycle). There were no possible differences in associated symptoms between the treatment groups in any time point considered except for the number of subjects presenting with diarrhea at the second and third cycles, which was greater among the meloxicam 15 mg group than the others (*P* values not reported). However, diarrhea also decreased in incidence in the meloxicam 15 mg group when comparing baseline to the other two menstrual cycles (*P* value not reported). A significant number of subjects had already experienced improvement in symptoms 2 hours after the study drug administration (*P* value not reported). There was a reduction from baseline in disability to work and disability to perform daily activities in all three treatment groups as measured by VAS scale (*P* values not reported).There were no differences between the treatment groups (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Tolerability to the treatment was rated better among subjects who received meloxicam than among those receiving mefenamic acid. These differences were significant when comparing the assessments of global tolerability by the investigator (*P* values not reported). The highest percentage of patients with an adverse event was seen in the mefenamic acid 1,500mg treatment arm. (*P* values not reported). There was no difference in the number of adverse events between the two doses of meloxicam (*P* values not reported). Gastrointestinal disorders were the most common adverse events reported for all three treatment arms. There were no out-of-range laboratory measurements reported by the investigators as clinically significant or any differences measured across the three treatment groups (*P* values not reported).
Sprains and Contusions				
Galer et al[24] Diclofenac epolamine 1.3% patch vs placebo patch	DB, MC, RCT, PC Patients 18 to 78 years of age, who had experienced a sports-related sprain, strain, or contusion less than 72 hours prior to study entry and reported at least 5 out of 10 on a pain scale or 50 mm out of 100 mm on a VAS	N=222 2 weeks	Primary: Pain experienced in the course of normal activities as measured by VAS, 5-item scale rating functionality, 4-item scale for skin irritation, swelling, and joint active range of motion and pain in daily diary outcomes as measured by 100 mm VAS, 5 item scale for pain and 5 item scale for functional improvement Secondary: Adverse events	Primary: There was a statistically significantly difference favoring diclofenac epolamine over placebo seen at days 3 and 14 (*P*=0.036, *P*=0.048 respectively) for pain and functioning variables. Diclofenac epolamine was favored for "summed pain intensity" on days 3, 7 and 14 (*P*≤0.044) as measured by daily diary assessments. Tolerability tests assessed by investigator favored diclofenac epolamine over placebo on days 7 and 14 (*P*=0.034, and *P*=0.014) and by patients on day 3 (*P*=0.021). Secondary There was no difference in adverse events between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Predel et al[25] Diclofenac sodium 140 mg patch (Olfen® patch‡) vs placebo patch	DB, MC, RCT Patients18 to 60 years of age were enrolled within 3 hours of an impact injury	N=120 7 days	Primary: AUC of tenderness over first 3 days Secondary: AUC of tenderness over 7 days, time to resolution of pain, efficacy assessment by patient and investigator on 4-point scale and adverse events, including hematological markers and vital signs	Primary: Diclofenac sodium patch was found to be significantly more effective than placebo at day 3 and at day 7 than placebo (*P*<0.0001). Secondary: More patients in the treatment group (73.3%) achieved pain resolution than in the placebo group (6.7%) at 7 days (*P*<0.0001). Significantly more patients in the treatment group had a score of "excellent" or "good" on the efficacy scale, as rated by investigators and patients (*P*<0.0001). No difference in adverse events was found between the two treatment groups.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, R=randomized, RCT=randomized controlled trial, RB=relative benefit, RR=relative risk, SD=standard deviation, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: ACR=American College of Rheumatology, ADL=activities of daily living, APAP=acetaminophen, ASA=aspirin, AUC=area under the curve, AUSCAN=Australian/Canadian Osteoarthritis Hand Index, C-HAQ= Childhood Health Assessment Questionnaire, COX-2=cyclooxygenase type 2, ESR=Westergren erythrocyte sedimentation rate, JIA=juvenile idiopathic arthritis, LBP=low back pain, MDHAQ=Multidimensional Health Assessment Questionnaire, NSAID=nonsteroidal anti-inflammatory drug, POM=pain on movement, SF-36=short form 36, VAS=visual acuity scale, WOMAC=Western Ontario and McMaster Universities
* Juvenile idiopathic arthritis is a newer term that includes all arthritis presentations in children. This term includes juvenile rheumatoid arthritis and also forms of "idiopathic" arthritis that occur in children.[1]
† Juvenile Idiopathic Arthritis core set values
- Number of joints with active arthritis [pain and limitation on movement range 0–75]
- Number of joints with limited range of motion [range 0–67]
- Physician's global evaluation of disease activity on a 100-mm VAS
- Parent's global assessment of the child's overall well-being on 100-mm VAS as reported on the C-HAQ
- Disability index of the C-HAQ
- ESR

‡ Agent not available in the United States.
§ Trial is registered on ClinicalTrials.gov.

Special Populations

Table 5. Special Populations[2-23]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Diclofenac epolamine	No dosage adjustment required in the elderly. Not studied in the pediatric population.	Caution advised.	Caution advised.	B	Unknown
Diclofenac potassium	Caution advised when used in the elderly. Not studied in the pediatric population.	Caution advised.	Caution advised.	C	Unknown
Diclofenac sodium	Caution advised when used in the elderly. Not studied in the pediatric population.	Caution advised.	Caution advised.	C	Unknown
Etodolac	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. Immediate-release formulation not studied in the pediatric population. Extended-release formulation can be used in children with juvenile rheumatoid arthritis 6 to 16 years of age based on data from adult studies.	Caution advised.	Dosage should be reduced in hepatic failure.	C	Unknown
Fenoprofen calcium	Caution advised when used in the elderly. Not studied in the pediatric population.	No dosage adjustment required.	Caution advised.	B (D in third trimester or near delivery)	Unknown
Flurbiprofen	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. Not studied in the pediatric population.	Caution advised.	Caution advised.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ibuprofen	Dosage adjustment not required. Prescription ibuprofen has not been studied in the pediatric population. Over-the-counter formulations are approved for children ages 6 months to 11 years.	Caution advised.	Caution advised.	C	In limited studies, not isolated in breast milk; however, risk to the infant cannot be ruled out.
Indomethacin	Doses higher than 150 to 200 mg/day have been associated with increased adverse effects in the elderly without a corresponding increase in clinical benefits. Safety and efficacy in children ≤14 years of age has not been established. If the drug is used in children ≥2 years of age, caution is advised. There have been cases of hepatic jaundice, including fatalities in children treated for juvenile rheumatoid arthritis.	Caution is advised. Treatment not recommended in patients with advanced renal disease.	Caution advised.	C (D after 34 weeks of gestation or near delivery)	Yes (% not reported)
Ketoprofen	Caution advised when used in the elderly. Elderly patients may have reduced renal function leading to accumulation of drug and increased risk of toxicity. Not studied in the pediatric population.	Renal dose adjustment required.	Hepatic dose adjustment required.	C	Unknown
Ketorolac tromethamine	Dosage adjustment required.	Contraindicated	Caution advised.	C	Yes (% not

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Not studied in the pediatric population.		Should be discontinued if liver function tests are abnormal after therapy initiation.		reported)
Meclofenamate	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. Safety below the age of 14 years has not been established.	Renal dose adjustment required.	Caution advised.	C	Yes (% not reported)
Mefenamic acid	Caution advised when used in the elderly. Safety below the age of 14 years has not been established.	Caution advised.	Hepatic dose adjustment required.	C	Yes (% not reported)
Meloxicam	Caution advised when used in the elderly. Approved for use in children 2 to 17 years of age.	Caution advised. Treatment is not recommended in patients with advanced renal disease.	Caution advised.	C	Unknown
Nambumetone	Caution advised when used in the elderly. Not studied in the pediatric population.	Renal dose adjustment required.	Caution advised.	C	Unknown
Naproxen and naproxen sodium	Caution is advised when high doses are required and dosage adjustment may be required. Approved for use in children 2 to 17 years of age.	Caution advised.	Caution advised.	C	Unknown
Oxaprozin	Caution advised when used in the elderly as they may not tolerate side effects as well as	Renal dose adjustment required.	Caution advised.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	younger patients. Not studied in the pediatric population.				
Piroxicam	Caution advised when used in the elderly. Not studied in the pediatric population.	Caution advised.	Hepatic dose adjustment required.	C	Yes (1% to 3%)
Sulindac	Caution advised when used in the elderly as they may not tolerate side effects as well as younger patients. Not studied in the pediatric population.	Renal dose adjustment required.	Hepatic dose adjustment required.	C	Unknown
Tolmetin sodium	No dose adjustment required. Approved for use in children 2 to 17 years of age.	Renal dose adjustment required.	Caution advised.	C	Yes (% not reported)
Combination Products					
Diclofenac sodium/ misoprostol	No dosage adjustment required in the elderly. Not studied in the pediatric population.	Caution advised.	Caution advised.	X	Yes (% not reported) (diclo-fenac) unknown (miso-prostol)

Adverse Drug Events

The adverse event profiles of nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly related to their effects on prostaglandin synthesis. This includes common gastrointestinal adverse events including dyspepsia and nausea. More serious adverse effects can include gastrointestinal ulceration and bleeding, worsening of heart failure and acute renal failure. The common adverse drug events (>1%) associated with NSAID therapy are included below in table 6.

Table 6. Adverse Drug Events[2-23]

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
Cardiovascular System																			
Angina/angina pectoris	-	1-2*	-	-	< 1	-	-	-	-	-	-	< 2	< 1	-	-	-	-	-	-
Arrhythmia	-	-	< 1	-	< 1	< 1	< 1	< 1	-	-	< 1	< 2	< 1	-	-	< 1	< 1	-	-
Hypertension	-	< 1 1-2*	< 1	-	< 1	< 1	< 1	< 1	1-3	-	< 1	< 2	< 1	-	-	< 1	< 1	3-9	1-3
Hypotension	-	< 1	-	-	-	-	< 1	-	-	-	< 1	< 2	-	-	-	< 1	-	-	-
Myocardial infarction	-	< 1	< 1	-	< 1	-	-	< 1	-	-	< 1	< 2	< 1	-	-	< 1	-	-	<2
Palpitations	-	< 1	< 1	2.5	-	< 1	< 1	< 1	< 1	< 1	< 1	< 2	< 1	1-3	< 1	< 1	< 1	-	-
Syncope	-	-	< 1	-	-	-	< 1	-	< 1	-	< 1	< 2	< 1	-	-	< 1	< 1	-	-
Tachycardia	-	< 1	-	< 1	-	-	< 1	< 1	-	-	< 1	< 2	-	-	-	< 1	-	-	-
Vasculitis	-	-	< 1	-	-	-	-	-	-	-	< 1	< 2	< 1	< 1	-	-	-	-	-
Central Nervous System																			
Abnormal dreams/ dream abnormalities	-	-	-	-	-	< 1	-	-	< 1	-	< 1	< 2	-	< 1	-	< 1	-	-	-
Anxiety	-	< 1	-	-	-	-	< 1	-	-	-	< 1	< 2	< 1	-	-	< 1	-	-	-
Asthenia/malaise	-	< 1	3-9	1-5.4	-	-	-	-	< 1	< 1	< 1	< 2	< 1	< 1	< 1	< 1	-	3-9	-
Central nervous system inhibition or excitation-	-	-	-	-	1-3	-	-	3-9	-	-	-	-	-	-	1-3	-	-	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
Confusion	-	-	< 1	1.4	< 1	< 1	< 1	< 1	-	-	< 1	< 2	< 1	-	-	< 1	-	-	-
Convulsions	-	< 1	-	-	< 1	-	< 1	-	-	-	< 1	< 2	-	-	-	< 1	< 1	-	-
Depression	-	< 1	1-3	< 1	-	< 1	1-3	-	< 1	< 1	< 1	< 2	< 1	< 1	-	< 1	< 1	1-3	-
Dizziness	-	1-3	3-9	6.5	1-3	3-9	3-9	1-3	7	3-9	1-10	1.1-3.8	3-9	3-9	-	1-10	3-9	3-9	3-4
Drowsiness	-	< 1	-	-	-	-	< 1	-	6	-	< 1	-	-	3-9	-	< 1	-	1-3	-
Fatigue	-	-	-	1.7	-	-	1-3	-	-	< 1	-	< 2	1-3	-	-	-	-		-
Headache	2	3-9 0-7*	< 1	8.7	3-9	1-3	11.7	3-9	17	3-9	1-10	2.4-8.3	3-9	3-9	-	1-10	3-9	3-9	3-7
Hypesthesia	-	-	0-3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypokinesia	-	0-2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insomnia	-	< 1	< 1	< 1	-	< 1	< 1	-	< 1	< 1	< 1	≤ 3.6	1-3	< 1	-	< 1	< 1	-	-
Lightheadedness	-	-	-	-	-	-	< 1	-	-	-	-	-	-	1-3	-	-	-	-	-
Nervousness	-	-	1-3	5.7	1-3	1-3	< 1	-	< 1	-	< 1	< 2	1-3	-	-	< 1	1-3	-	-
Paresthesia	1	< 1 8-20*	< 1	-	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 2	< 1	-	-	< 1	< 1	-	-
Somnolence	1	-	< 1	8.5	-	< 1	1-3	-	-	-	< 1	< 2	1-3	-	-	< 1	< 1	-	-
Tremor	-	< 1	-	2.2	-	-	-	-	< 1	-	< 1	< 2	< 1	-	-	< 1	-	-	-
Vertigo	-	-	-	-	-	-	1-3	< 1	< 1	-	< 1	2	< 1	1-3	-	< 1	< 1	-	-
Dermatological																			
Alopecia/loss of hair	-	< 1 1-2*	< 1	< 1	< 1	< 1	< 1	< 1	-	< 1	< 1	< 2	< 1	< 1	< 1	< 1	< 1	-	-
Bullous eruption/rash	-	< 1 0-4*	-	-		-	-	< 1	-	-	-	< 2	< 1	-	-	-	-	-	-
Burning/pain	< 1	15-26*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dry skin	-	25-27*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Edema	-	3-4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Exfoliation	-	6-24*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
Exfoliative dermatitis	2	< 1 0-2*	-	< 1	< 1	-	< 1	< 1	-	< 1	< 1	-	-	-	< 1	< 1	< 1	-	-
Increased sweating	-	< 1	< 1	4.6	< 1	-	< 1	< 1	1-3	-	< 1	< 2	1-3	1-3	-	< 1	-	-	-
Photosensitivity/ photosensitivity reaction	-	< 1 0-3*	< 1	-	< 1	-	-	< 1	-	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	-	-
Pruritus	5	1-3 31-52*	1-4	4.2	< 1	1-3	< 1	< 1	1-3	1-3	1-10	≤ 2.4	3-9	3-9	< 1	1-10	1-3	-	-
Rash	-	1-3 35-46*	1-3	3.7	1-3	3-9	< 1	1-3	1-3	3-9	1-10	0.3-3	3-9	< 1	3-9	1-10	3-9	-	<5
Skin carcinoma	-	0-2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin eruptions	-	-	-	-	-	-	-	-	-	-	-	-	-	3-9	-	-	-	-	-
Skin irritation	-	19-33*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1-3	-
Skin ulcer	-	1-2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urticaria	-	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	1-3	< 1	< 2	< 1	< 1	< 1	< 1	-	< 1	-
Gastrointestinal																			
Abdominal distension	-	1-3	-	-	-	-	< 1	-	-	-	-	-	-	-	-	-	-	-	-
Abdominal/ gastrointestinal distress	-	-	-	-	-	1-3	1-3	-	-	-	-	-	-	-	1-3	-	-	3-9	-
Abdominal pain or cramps	-	3-9 1-2*	3-9	2	3-9	1-3	1-3	3-9	-	3-9	1-10	1.9-4.7	12	3-9	1-3	1-10	10 (pain) 1-3 (cramps)	3-9	21
Anorexia/decreased appetite	-	-	< 1	< 1	-	1-3	< 1	1-3	< 1	1-3	-	-	< 1	-	1-3	1-10	1-3	-	-
Appetite increase	-	-	-	-	-	-	-	<1	<1	-	-	<2	<1	-	-	-	-	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	**Diclofenac epolamine**	**Diclofenac sodium/ potassium**	**Etodolac**	**Fenoprofen**	**Flurbiprofen**	**Ibuprofen**	**Indomethacin**	**ketoprofen**	**ketorolac**	**Meclofenamate**	**Mefenamic acid**	**Meloxicam**	**Nabumetone**	**Naproxen/na-proxen sodium**	**Oxaprozin**	**Piroxicam**	**Sulindac**	**Tolmetin Sodium**	**Diclofenac sodium/ misoprostol**
Bloating	-	-	-	-	-	1-3	< 1	-	-	-	-	-	-	-	-	-	-	-	-
Colitis	-	<1	<1	-	<1	-	-	-	-	<1	-	<2	-	<1	-	-	<1	-	-
Constipation	-	3-9	1-3	7	1-3	1-3	1-3	3-9	1-3	1-3	1-10	0.8-2.6	3-9	3-9	3-9	1-10	3-9	1-3	-
Diarrhea	-	3-9 2*	3-9	1.8	3-9	1-3	1-3	3-9	7	10-33	1-10	1.9-7.8	14	1-3	3-9	1-10	3-9	3-9	19
Dry mouth	-	<1	<1	<1	<1	<1	-	<1	<1	-	<1	<2	1-3	-	-	<1	-	-	-
Dysgeusia	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia/ Indigestion	7	3-9 2-3*	10	10.3	3-9	1-3	3-9	11	12	-	1-10	3.8-9.5	13	1-3	3-9	1-10	3-9	3-9	14
Epigastric/ gastrointestinal pain	-	-	-	-	-	3-9	-	-	13	-	-	-	-	-	-	-	-	-	-
Eructation	-	-	<1	-	-	-	-	<1	<1	-	<1	<2	<1	-	-	<1	-	-	-
Esophagitis	-	-	<1	-	-	-	-	-	-	-	<1	<2	-	-	-	<1	-	-	-
Flatulence	-	1-3	3-9	< 1	1-3	1-3	< 1	3-9	1-3	3-9	1-10	0.4-3.2	3-9	-	1-3	1-10	1-3	3-9	9
Gastritis	-	-	1-3	< 1	< 1	< 1	-	< 1	< 1	-	< 1	< 2	1-3	-	-	< 1	< 1	1-3	-
Gastrointestinal bleeding	-	0.6	-	< 1	1-3	< 1	-	-	-	-	< 1	< 2	< 1	< 1	< 1	-	< 1	< 1	1-4
Gastrointestinal fullness	-	-	-	-	-	1-3	-	-	1-3	-	-	-	-	-	-	-	-	-	-
Gross bleeding/ perforation	-	-	-	-	-	-	-	-	-	-	1-10	-	-	-	-	1-10	-	-	1-4
Heartburn	-	-	-	-	-	3-9	-	-	-	3-9	1-10	-	-	3-9	-	1-10	-	-	-
Hematemesis	-	-	-	-	<1	-	-	<1	-	-	<1	<2	-	<1	-	<1	-	-	-
Hepatitis	-	<1	<1	-	<1	<1	-	<1	-	-	<1	<2	-	-	<1	<1	<1	<1	1-3
Melena	-	< 1	1-3	-	-	< 1	-	< 1	-	-	< 1	< 2	< 1	< 1	-	< 1	-	-	-
Nausea	-	3-9	3-9	7.7	3-9	3-9	3-9	3-9	12	11	1-10	2.4-7.2	3-9	3-9	3-9	1-10	3-9	11	11
Nausea and vomiting	17	-	-	-	-	1-3	1-3	-	-	11	-	-	-	-	-	-	1-3	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
Pancreatitis	-	<1	<1	<1	-	<1	-	<1	-	-	<1	<2	<1	<1	<1	<1	<1	-	-
Peptic ulcer	-	0.6	<1	<1	<1	-	<1	<1	-	1-3	1-10	<2	<1	-	<1	1-10	<1	1-3	0-9
Peptic ulcer bleed	-	1-3	< 1	-	-	< 1	-	-	-	-	-	< 2	-	-	< 1	-	-	-	-
Positive stool guaiac	-	-	-	< 1	-	-	-	-	-	-	-	-	3-9	-	-	-	-	-	-
Stomatitis	-	-	-	-	< 1	-	-	1-3	1-3	1-3	< 1	-	1-3	1-3	< 1	< 1	< 1	< 1	-
Vomiting	-	< 1	1-3	2.6	1-3	-	-	1-3	1-3	-	1-10	0.6-2.6	1-3	< 1	1-3	1-10	-	3-9	-
Genitourinary																			
Albuminuria	-	-	-	-	-	-	-	-	-	-	-	< 2	< 1	-	-	-	-	-	-
Dysuria	-	-	1-3	< 1	-	-	-	-	-	-	< 1	-	< 1	-	1-3	< 1	< 1	< 1	-
Hematuria	-	< 1 0-2*	< 1	< 1	< 1	< 1	< 1	< 1	< 1	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	-
Renal failure	-	-	< 1	< 1	< 1	-	< 1	< 1	-	< 1	< 1	< 2	< 1	< 1	-	< 1	< 1	< 1	-
Renal function impairment/ insufficiency	-	-	< 1	-	-	-	< 1	3-9	-	-	1-10	-	-	-	< 1	1-10	< 1	-	-
Urinary frequency/ polyuria	-	< 1	1-3	-	-	< 1	< 1	-	< 1	-	< 1	0.1-2.4	-	-	1-3	< 1	-	-	-
Urinary tract infection/ symptoms	-	-	-	-	3-9	-	-	1-3	-	-	-	0.3-6.9	-	-	-	-	-	1-3	-
Hematologic/Lymphocytic																			
Anemia	-	-	< 1	-	-	-	-	< 1	< 1	-	1-10	≤ 4.1	< 1	-	< 1	1-10	-	-	1-3
Ecchymosis	-	-	< 1	-	< 1	-	< 1	-	-	-	< 1	-	-	3-9	< 1	< 1	< 1	-	-
Leukopenia	-	< 1	< 1	-	< 1	-	< 1	-	-	< 1	< 1	< 2	< 1	< 1	< 1	< 1	< 1	-	-
Purpura	-	< 1	-	< 1	-	-	-	< 1	1-3	-	< 1	< 2	-	1-3	-	< 1	< 1	< 1	-
Thrombocytopenia	-	< 1	< 1	< 1	< 1	< 1	-	< 1	-	-	< 1	< 2	< 1	< 1	< 1	< 1	< 1	< 1	-
Hypersensitivity																			
Allergy/allergic	-	0-1*	< 1	-	-	-	-	< 1	-	-	-	< 2	-	-	-	-	-	-	-

Adverse reaction (%)	Single Entity Products																		Com-bination Products
	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
reaction																			
Angioedema/ angioneurotic edema	-	< 1	< 1	< 1	< 1	< 1	< 1	-	-	-	< 1	< 2	< 1	< 1	-	< 1	< 1	-	-
Lab Test Abnormalities																			
ALT or AST elevations	-	2 0-3*	-	< 1	-	-	-	-	-	-	-	< 2	-	-	-	-	-	-	7-12
Bleeding time increased	-	-	< 1	-	-	-	-	-	-	-	1-10	-	-	-	-	1-10	-	-	-
Blood urea nitrogen increased	-	-	< 1	-	-	-	< 1	3-9	-	-	-	< 2	-	-	-	-	-	1-3	-
Creatinine increase	-	0-4*	< 1	-	-	-	-	-	-	-	-	< 2	-	-	-	-	-	-	1
Hemoglobin and hematocrit decreases	-	< 1	-	-	< 1	< 1	-	-	-	< 1	-	-	-	-	-	-	-	1-3	-
Hypercholesterolemia	-	0-3*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liver test abnormalities/ elevations	-	3-9	< 1	-	1-3	< 1	-	-	-	< 1	1-10	-	< 1	< 1	< 1	1-10	< 1	< 1	-
Metabolic and Nutritional																			
Body weight changes	-	-	< 1	-	1-3	-	-	< 1	-	-	< 1	< 2	-	-	< 1	< 1	-	3-9	-
Edema	-	-	< 1	-	3-9	1-3	< 1	3-9	4	1-3	1-10	0.5-4.5	3-9	3-9	< 1	1-10	1-3	3-9	-
Fluid retention	-	1-3	-	-	-	1-3	< 1	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral edema	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thirst	-	-	< 1	-	-	-	-	< 1	-	-	-	-	-	1-3	-	-	-	-	-
Musculoskeletal System																			
Arthralgia	-	0-2*	-	-	-	-	-	-	-	-	-	≤ 5.3	-	-	-	-	-	-	-
Back pain	-	2-4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Muscle weakness	-	0-2*	-	-	-	-	< 1	-	-	-	-	-	-	< 1	-	-	< 1	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	Diclofenac epolamine	Diclofenac sodium/ potassium	Etodolac	Fenoprofen	Flurbiprofen	Ibuprofen	Indomethacin	ketoprofen	ketorolac	Meclofenamate	Mefenamic acid	Meloxicam	Nabumetone	Naproxen/na-proxen sodium	Oxaprozin	Piroxicam	Sulindac	Tolmetin Sodium	Diclofenac sodium/ misoprostol
Myalgia	-	2-3*	-	-	-	-	-	< 1	-	-	-	-	-	< 1	-	-	-	-	-
Respiratory System																			
Asthma	-	< 1 0-2*	< 1	-	< 1	-	< 1	-	-	-	< 1	< 2	< 1	-	-	< 1	-	-	-
Bronchospasm	-	-	-	-	-	< 1	-	< 1	-	-	-	< 2	-	-	-	-	< 1	-	-
Coughing	-	-	-	-	-	-	-	-	< 1	-	-	0.2-2.4	< 1	-	-	-	-	-	-
Dyspnea	-	< 1 2*	< 1	2.8	< 1	-	< 1	< 1	< 1	-	< 1	< 2	< 1	3-9	-	< 1	< 1	-	-
Pharyngitis	-	2*	< 1	-	-	-	-	< 1	-	-	-	0.6-3.2	-	-	-	-	-	-	-
Pneumonia	-	0-2*	-	-	-	-	-	-	-	-	< 1	-	-	-	-	< 1	-	-	-
Rhinitis	-	2*	< 1	-	1-3	< 1	-	< 1	< 1	-	-	-	-	-	-	-	-	-	-
Sinusitis	-	0-2*	< 1	-	-	-	-	-	-	-	-	-	-	-	< 1	-	-	-	-
Upper respiratory infection	-	-	-	1.5	-	-	-	-	-	-	-	≤ 8.3	-	-	< 1	-	-	-	-
Other																			
Accident, household	-	-	-	-	-	-	-	-	-	-	-	3.2-4.5	-	-	-	-	-	-	-
Back pain	-	-	-	-	-	-	-	-	-	-	-	0.4-3	-	-	-	-	-	-	-
Blurred vision	-	< 1	1-3	2.2	-	-	< 1	-	< 1	< 1	< 1	-	-	-	< 1	< 1	< 1	-	-
Chest pain	-	< 1	-	-	-	-	< 1	-	-	-	-	-	-	-	-	-	-	1-3	-
Chills	-	-	1-3	-	< 1	-	-	< 1	-	-	-	-	< 1	< 1	-	-	-	-	-
Conjunctivitis	-	2-4*	< 1	-	< 1	< 1	-	< 1	-	< 1	< 1	< 2	-	-	< 1	< 1	-	-	-
Face edema	-	-	-	-	-	-	-	< 1	-	-	-	< 2	-	-	-	-	-	-	-
Fall	-	-	-	-	-	-	-	-	-	-	-	≤ 2.6	-	-	-	-	-	-	-
Fever	-	-	1-3	< 1	< 1	-	< 1	-	< 1	-	< 1	< 2	< 1	< 1	-	< 1	-	< 1	-
Hearing disturbances	-	-	-	-	-	-	< 1	-	-	-	-	-	-	1-3	-	-	-	-	-
Hearing loss/ impairment	-	< 1	-	1.6	-	< 1	-	< 1	< 1	-	< 1	-	-	< 1	< 1	< 1	< 1	-	-

	Single Entity Products																		Com-bination Products
Adverse reaction (%)	**Diclofenac epolamine**	**Diclofenac sodium/ potassium**	**Etodolac**	**Fenoprofen**	**Flurbiprofen**	**Ibuprofen**	**Indomethacin**	**ketoprofen**	**ketorolac**	**Meclofenamate**	**Mefenamic acid**	**Meloxicam**	**Nabumetone**	**Naproxen/na-proxen sodium**	**Oxaprozin**	**Piroxicam**	**Sulindac**	**Tolmetin Sodium**	**Diclofenac sodium/ misoprostol**
Infection	-	4*	< 1	-	-	-	-	< 1	< 1	-	< 1	-	-	-	-	< 1	-	-	-
Influenza-like disease/ symptoms	-	1-10*	-	-	-	-	-	-	-	-	-	4.5-5.8	-	-	-	< 1	-	-	<5
Injury, accidental	-	0-4*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neck pain	-	0-2*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	-	-	-	-	< 1	-	-	-	0.9-5.2	-	-	-	-	-	-	-
Taste disorder/ perversion/ disturbance/alteration/ changes	-	< 1	< 1	-	< 1	-	-	< 1	-	< 1	-	< 2	< 1	-	< 1	-	-	-	-
Tinnitus	-	1-3	1-3	4.5	1-3	1-3	1-3	1-3	< 1	1-3	1-10	< 2	3-9	3-9	1-3	1-10	1-3	1-3	-
Visual disturbances/ changes	-	-	< 1	-	1-3	-	-	1-3	-	-	-	-	< 1	1-3	-	-	< 1	1-3	-

ALT=alanine aminotransferase, AST=aspartate transaminase
*Topical dosage form.
- Event not reported.

Contraindications/Precautions[2-23]

All nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with a known hypersensitivity to the NSAID, or who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or an NSAID. Additionally, NSAID use is associated with gastrointestinal and cardiovascular risks which have led to the black box warning included below.

Black Box Warning for Nonsteroidal Anti-inflammatory Drugs

WARNING
Cardiovascular Risk
• NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. • NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
Gastrointestinal Risk
• NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.

Fenoprofen: Fenoprofen is contraindicated for use in the setting of preexisting renal disease.

Indomethacin: Indomethacin suppositories are contraindicated in patients with a history of proctitis or recent rectal bleeding.

Ketorolac: Ketorolac's contraindications include: active peptic ulcer disease; recent gastrointestinal bleeding or perforation; a history of peptic ulcer disease or gastrointestinal bleeding; advanced renal impairment or patients at risk for renal failure because of volume depletion; use in labor and delivery; use in nursing mothers; as prophylactic analgesic before any major surgery; intraoperatively use when hemostasis is critical; suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding; patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events; neuraxial (epidural or intrathecal) administration; and concomitant use with probenecid. These risks have led to the black box warning included below.

Black Box Warning for Ketorolac

WARNING
• Ketorolac is indicated for the short-term (up to 5 days) management of moderately severe acute pain that requires analgesia at the opioid level in adults. It is not indicated for minor or chronic painful conditions. Ketorolac is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse reactions can be serious in certain patients for whom ketorolac is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse reactions. • Ketorolac can cause peptic ulcers, GI bleeding, or perforation. Therefore, it is contraindicated in patients with active peptic ulcer disease, in patients with recent GI bleeding or perforation, and in patients with a history of peptic ulcer disease or GI bleeding. • Ketorolac is contraindicated in patients with advanced renal function impairment or in patients at risk for renal failure due to volume depletion. • Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and those at high risk of bleeding.

WARNING
• Ketorolac is contraindicated as prophylactic analgesic before any major surgery and is contraindicated intraoperatively when hemostasis is critical because of the increased risk of bleeding. • Hypersensitivity reactions ranging from bronchospasm to anaphylactic shock have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac intravenous (IV)/intramuscular (IM). Ketorolac is contraindicated in patients who have previously demonstrated hypersensitivity to ketorolac or allergic manifestations to aspirin or other NSAIDs. • Ketorolac is contraindicated for neuraxial (epidural or intrathecal) administration because of its alcohol content. • Ketorolac is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions. • The use of ketorolac is contraindicated in breast-feeding mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates. • Ketorolac is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse reactions. • Oral ketorolac is indicated only as continuation therapy to ketorolac IV/IM, and the combined duration of use of ketorolac IV/IM and oral ketorolac is not to exceed 5 days because of the increased risk of adverse reactions. • The recommended total daily dose of ketorolac oral (maximum 40 mg) is significantly lower than that for ketorolac IV/IM (maximum 120 mg). • Ketorolac dosage should be adjusted for patients 65 years of age and older, for patients less than 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine. Doses of ketorolac IV/IM are not to exceed 60 mg (total dose per day) in these patients. Ketorolac is indicated as a single-dose therapy in pediatric patients, not to exceed 30 mg for IM administration and 15 mg for IV administration.

Mefenamic acid: Contraindications include active ulceration or chronic inflammation of either the upper or lower gastrointestinal tract and use in the setting of preexisting renal disease.

Drug Interactions

Table 7. Drug Interactions[1-23]

Generic Name	Interacting Medication or Disease	Potential Result
Nonsteroidal anti-inflammatory drugs (NSAIDs) (all)	Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs)	NSAIDs may decrease the antihypertensive effect of ACE inhibitors and ARBs and could precipitate renal failure. Monitor blood pressure and for hyperkalemia or acute renal failure.
NSAIDs (all)	Antiplatelet agents, clopidogrel, low molecular weight heparins, gingko biloba, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, warfarin	NSAIDs used concurrently with the interacting medication may result in an increased risk of bleeding. Monitor closely for bleeding, particularly gastrointestinal bleeding, which may be serious.
NSAIDs (all)	Aspirin	NSAIDs may reduce the cardioprotective effect of low-dose uncoated aspirin and may cause a higher risk of gastric irritation. Administer ibuprofen at least 8 hours before or 30 minutes after immediate-release aspirin. Administer an NSAID at least 1 hour after taking enteric-coated aspirin for cardioprotective action. Ketorolac is contraindicated for use with aspirin due to an increased risk of

Generic Name	Interacting Medication or Disease	Potential Result
		gastrointestinal adverse effects.
NSAIDs (all)	Azole antifungals (fluconazole, voriconazole)	Azole antifungals may increase the concentration of NSAIDs through CYP2C9 inhibition. Observe patients for an increase in NSAID adverse reactions and adjust the NSAID dose as needed.
NSAIDs (all)	Cyclosporine	NSAIDs used concurrently with cyclosporine may lead to additive nephrotoxicity. Monitor renal function.
NSAIDs (all)	Ketorolac	NSAIDs used concurrently with ketorolac may result in enhanced gastrointestinal adverse effects. This combination is contraindicated.
NSAIDs (all)	Loop diuretics, potassium sparing diuretics, thiazide diuretics	NSAIDs may reduce the effectiveness of diuretics and cause hyperkalemia or nephrotoxicity. Monitor blood pressure, weight changes, urine output, potassium levels, and creatinine levels.
NSAIDs (all)	Quinolone antibiotics	Concurrent use of NSAIDs and quinolone antibiotics may result in an increased risk of seizures. Caution is advised.
NSAIDs (all)	Sulfonylureas	NSAIDs used concurrently with sulfonylureas may result in an increased risk of hypoglycemia. Monitor closely for hypoglycemia.
NSAIDs (all)	Tacrolimus	NSAIDs used concurrently with tacrolimus may lead to additive nephrotoxicity resulting in acute renal failure. Monitor renal function.
NSAIDs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin sodium)	Methotrexate	NSAIDs used concurrently with methotrexate may result in methotrexate toxicity. Do not administer NSAIDs within 10 days of high-dose methotrexate. If concomitant administration is necessary, monitor closely for toxicity, especially myelosuppression and gastrointestinal toxicity. Lower doses have been tolerated with NSAID therapy, however caution is advised.
NSAIDs (indomethacin, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, tolmetin sodium)	Lithium	Concurrent use of indomethacin and lithium may result in an increased risk of lithium toxicity (weakness, tremor, excessive thirst, confusion). Monitor serum lithium levels for any symptoms of lithium toxicity.
NSAIDs (ibuprofen,	Beta-blockers	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce

Generic Name	Interacting Medication or Disease	Potential Result
indomethacin, naproxen, piroxicam)		hypertension and impair the antihypertensive effect of beta-blockers. Avoid using interacting NSAIDs if possible. Monitor blood pressure and adjust dose as needed.
NSAIDs (diclofenac, indomethacin)	Digoxin	NSAIDs used concurrently with digoxin may result in an increased risk of digoxin toxicity (nausea, vomiting and arrhythmias). Monitor the patient for signs of digoxin toxicity and if digoxin toxicity is suspected a digoxin serum concentration should be determined.
NSAIDs (ibuprofen)	Phenytoin	Ibuprofen used concurrently with phenytoin may result in an increased risk of phenytoin toxicity, especially in renally impaired patients. Monitor phenytoin serum concentrations and for signs and symptoms of phenytoin toxicity.
NSAIDs (indomethacin)	Potassium	Indomethacin used concurrently with potassium supplementation may result in hyperkalemia. Monitor serum potassium and if necessary discontinue potassium supplementation or decrease indomethacin dose.

Dosage and Administration

The recommended dosing of the nonsteroidal anti-inflammatory drugs (NSAIDs) is outlined below in Table 8. When available, the recommended maximum dose is included in the table.

Table 8. Dosing and Administration[2-23]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Diclofenac epolamine	Mild to moderate pain: Transdermal patch: initial and maintenance, apply 1 patch to the most painful area twice a day	Safety and efficacy has not been established in the pediatric population.	Transdermal patch: 1.3%
Diclofenac potassium	Ankylosing spondylitis: Tablet: initial and maintenance, 50 mg twice daily; maximum, 125 mg daily Mild to moderate pain: Tablet: initial and maintenance, 50 mg three times daily, in some patients 100 mg initially followed by 50 mg doses may provide better pain relief; maximum, 200 mg daily Primary dysmenorrhea: Tablet: initial and maintenance, 50 mg three times daily, in some patients 100 mg initially followed by 50 mg doses may provide better relief; maximum, 200 mg daily Osteoarthritis: Tablet: initial and maintenance, 100-150 mg daily in divided doses, 50 mg twice daily or three times daily; maximum, 200 mg daily	Safety and efficacy has not been established in the pediatric population.	Tablet: 50 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Rheumatoid arthritis: Tablet: initial and maintenance, 150-200 mg daily in divided doses, 50 mg three times or four times daily; maximum, 225 mg daily		
Diclofenac sodium	Osteoarthritis: Delayed-release tablet: initial and maintenance, 100-150 mg daily in divided doses, 50 mg two or three times daily or 75 mg twice daily Extended-release tablet: initial and maintenance, 100 mg daily Topical gel: initial and maintenance, apply 4 g to the affected foot, knee, or ankle 4 times daily; apply 2 g to the affected hand, elbow, or wrist 4 times daily; maximum, 8 g daily to any single joint of the upper extremities, 16 g daily to any single joint of the lower extremities and 32 g daily, over all affected joints Rheumatoid arthritis: Delayed-release tablet: initial and maintenance, 150-200 mg daily in divided doses, 50 mg three or four times daily or 75 mg twice daily Extended-release tablet: initial and maintenance, 100 mg daily, may be increased to 100 mg twice daily if there is an inadequate response Ankylosing spondylitis: Delayed-release tablet: initial and maintenance,100-125 mg daily in divided doses, 25 mg four times daily with an extra 25 mg dose at bedtime, if needed	Safety and efficacy has not been established in the pediatric population.	Delayed-release tablet: 25 mg 50 mg 75 mg Extended-release tablet: 100 mg Topical gel: 1%
Etodolac	Mild to moderate pain: Capsule and tablet: initial and maintenance, 200 to 400 mg every 6 hours; maximum, 1,200 mg daily Osteoarthritis and rheumatoid arthritis: Capsule and tablet: initial, 300 mg 2 or 3 times daily, 400 mg 2 times daily or 500 mg 2 times daily; maintenance, 600 mg daily may control symptoms long term; maximum, 1,200 mg daily Extended-release tablet: initial and maintenance, 400 to 1,000 mg once daily;	Juvenile rheumatoid arthritis: Extended-release tablet: initial and maintenance, once daily based on weight as follows: 20 to 30 kg should receive 400 mg daily, 31 to 45 kg should receive 600 mg daily, 46 to 60 kg should receive 800 mg daily, >60 kg	Capsule: 200 mg 300 mg Extended-release tablet: 400 mg 500 mg 600 mg Tablet: 400 mg 500 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	maximum, 1,200 mg daily	should receive 100 mg daily	
Fenoprofen calcium	Mild to moderate pain: Capsule: initial and maintenance, 200 mg every 4 to 6 hours as needed Osteoarthritis and rheumatoid arthritis: Capsule and tablet: initial and maintenance, 300 to 600 mg 3 or 4 times daily; maximum, 3,200 mg daily	Safety and efficacy has not been established in the pediatric population.	Capsule: 200 mg 300 mg Tablet: 600 mg
Flurbiprofen	Osteoarthritis and rheumatoid arthritis: Tablet: initial and maintenance: 200 to 300 mg daily administered 2, 3 or 4 times a day (no more than 100 mg as a single dose)	Safety and efficacy has not been established in the pediatric population.	Tablet: 50 mg 100 mg
Ibuprofen	Dysmenorrhea: Tablet: initial and maintenance, 400 mg every 4 hours as needed; maximum, 3,200 mg daily Mild to moderate pain: Tablet: initial and maintenance, 400 mg every 4 to 6 hours as needed; maximum, 3,200 mg daily Osteoarthritis and rheumatoid arthritis: Tablet: initial and maintenance, 300 mg 4 times daily; 400, 600, or 800 mg 3 or 4 times daily; maximum, 3,200 mg daily	Safety and efficacy of prescription strength ibuprofen has not been established in the pediatric population. Over the counter formulations are indicated in children for the treatment of minor pain and the reduction of fever.	Tablet: 400 mg 600 mg 800 mg
Indomethacin	Ankylosing spondylitis, osteoarthritis and rheumatoid arthritis: Capsule, suppository and suspension: initial, 25 mg 2 or 3 times daily; maintenance, increase the daily dosage by 25 or 50 mg; maximum, 200 mg daily Extended-release capsule: initial, 75 mg daily; maintenance, 75 mg twice daily; maximum, 150 mg daily Bursitis or tendonitis of the shoulder: Capsule, extended-release capsule and suspension: initial and maintenance, 75 to 150 mg daily (in 3 or 4 divided doses for capsule, suppository and suspension and 1 extended-release capsule twice daily if 150 mg daily is administered) Acute gouty arthritis: Capsule and suspension: initial: 50 mg 3 times a day until pain is tolerable; maintenance, after pain is tolerable dose should be rapidly reduced to complete cessation of the drug	Safety and efficacy has not been established in the pediatric population.	Capsule: 25 mg 50 mg Extended-release capsule: 75 mg Suppository: 50 mg Suspension: 25 mg/5 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
Ketoprofen	Dysmenorrhea and mild to moderate pain: Capsule: initial and maintenance, 25 to 50 mg every 6 to 8 hours as needed; maximum, 300 mg daily Osteoarthritis and rheumatoid arthritis: Capsule: initial and maintenance, 75 mg 3 times or 50 mg 4 times a day; maximum, 300 mg daily Extended-release capsule: initial and maintenance, 200 mg daily; maximum, 200 mg daily	Safety and efficacy has not been established in the pediatric population.	Capsule: 50 mg 75 mg Extended-release capsule: 100 mg 150 mg 200 mg
Ketorolac tromethamine	Moderately severe, acute pain: Injection: initial, single dose intramuscular (IM): Patients <65 years of age should be administered one 60 mg dose. Patients ≥65 years of age, renally impaired, or weighing <50 kg should be administered one 30 mg dose. Single dose intravenous (IV): Patients <65 years of age should be administered one 30 mg dose. Patients ≥65 years of age, renally impaired, or weighing <50 kg should be administered 1 dose of 15 mg. Multiple dose IV or IM: Patients <65 years of age should be administered 30 mg IV/IM every 6 hours. Patients ≥65 years of age, renally impaired, or weighing <50 kg and 15 mg IV/IM every 6 hours in; maintenance, not intended for use >5 days; maximum, 120 mg daily in patients< 65 years of age and 60 mg daily≥65 years of age, renally impaired, or weighing <50 kg Tablet: initial, patients <65 years of age: take 20 mg as first dose following 60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose. 10 mg every 4 to 6 hours thereafter; maintenance, not intended for use >5 days; maximum, 40 mg daily Patients >65 years of age, renally impaired, or weighing <50 kg: Take 10 mg as first dose following 30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose. 10 mg every 4 to 6 hours thereafter; maintenance, not intended for use >5 days; maximum, 40 mg daily	Safety and efficacy of oral ketorolac has not been established in the pediatric population. Moderately severe, acute pain: Injection: initial, one dose of 1 mg/kg (IM) or 0.5 mg/kg (IV); maintenance, only intended for use as a single dose; maximum, 30 mg (IM) or 15 mg (IV)	Injection: 15 mg/mL 30 mg/mL Tablet: 10 mg
Meclofenamate	Mild to moderate pain: Capsule: initial, 50 mg every 4 to 6 hours; maintenance, 100 mg may be required in some patients for optimal pain relief; maximum, 400 mg daily	Safety and efficacy has not been established in the pediatric population in patients <14 years of age.	Capsule: 50 mg 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Excessive menstrual blood loss and primary dysmenorrhea: Capsule: initial and maintenance, 100 mg 3 times daily for up to 6 days starting at the onset of menstrual flow; maximum, 400 mg daily Rheumatoid arthritis and osteoarthritis: Capsule: initial and maintenance, 200 to 400 mg daily, administered in 3 or 4 equal doses; maximum, 400 mg daily	Adolescent's ≥14 years of age may be treated using adult dosing.	
Mefenamic acid	Mild to moderate pain: Capsule: initial, 500 mg as an initial dose followed by 250 mg every 6 hours as needed; maintenance, therapy should usually not to exceed 1 week Primary dysmenorrhea: Capsule: initial, 500 mg as an initial dose followed by 250 mg every 6 hours, starting with the onset of bleeding and associated symptoms; maintenance, therapy should only be necessary for 2 to 3 days	Safety and efficacy has not been established in the pediatric population in patients <14 years of age. Adolescents aged 14 and above may be treated using adult dosing.	Capsule: 250 mg
Meloxicam	Osteoarthritis: Oral suspension and tablet: initial, 7.5 mg daily; maintenance, some patients may receive additional benefit by increasing to 15 mg daily; maximum, 15 mg daily Rheumatoid arthritis: Oral suspension and tablet: initial, 7.5 mg daily; maintenance, some patients may receive additional benefit by increasing to 15 mg daily; maximum, 15 mg daily	Juvenile Rheumatoid Arthritis: Oral suspension and tablet: initial and maintenance, 0.125 mg/kg once daily; maximum, 7.5 mg daily	Oral suspension: 7.5 mg/5 mL Tablet: 7.5 mg 15 mg
Nabumetone	Osteoarthritis and rheumatoid arthritis: Tablet: initial 1,000 mg taken as a single dose daily; maintenance, 1,500 to 2,000 mg daily given in either a single or twice-daily dose; maximum, 2,000 mg daily	Safety and efficacy has not been established in the pediatric population.	Tablet: 500 mg 750 mg
Naproxen	Ankylosing spondylitis, osteoarthritis and rheumatoid arthritis: Delayed-release tablet: initial and maintenance, 375 or 500 mg twice daily; maximum, 1,500 mg daily Oral suspension and tablet: initial, 250 mg twice daily; maintenance, 375 or 500 mg twice daily, maximum 1,500 mg daily Acute gout: Tablet: initial and maintenance, 750 mg followed by 250 mg every 8 hours; maximum, 1,500 mg daily	Juvenile rheumatoid arthritis: Oral suspension: initial and maintenance, 5 mg/kg given twice a day	Delayed-release tablet 375 mg 500 mg Oral suspension 125 mg/5 mL Tablet: 250 mg 375 mg 500 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Naproxen sodium	Ankylosing spondylitis, osteoarthritis and rheumatoid arthritis: Tablet and controlled-release tablet: initial and maintenance, 275 mg or 550 mg twice daily; maximum, 1,650 mg daily Acute bursitis and tendonitis: Tablet: initial and maintenance, 550 mg followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as needed; maximum, 1,650 mg daily Acute gout: Tablet: initial and maintenance, 825 mg followed by 275 mg every 8 hours; maximum, 1,650 mg daily	Safety and efficacy of naproxen sodium has not been established in the pediatric population. However, the naproxen oral suspension is indicated in the treatment of pediatric patients as noted above.	Controlled-release tablet: 412.5 mg (375 mg naproxen) 550 mg (500 mg naproxen) Tablet: 275 mg (250 mg naproxen) 550 mg (500 mg naproxen)
Oxaprozin	Osteoarthritis: Caplet and tablet: initial and maintenance, 600 mg once daily for mild to moderate osteoarthritis and 1,200 mg once daily for moderate to severe osteoarthritis; maximum, 1,800 mg daily or 26 mg/kg (whichever is lower) Rheumatoid arthritis: Caplet and tablet: initial and maintenance, 1,200 mg once daily, or in divided doses if once daily dosing is not tolerated; maximum, 1,800 mg daily	Safety and efficacy has not been established in the pediatric population.	Caplet: 600 mg Tablet: 600 mg 678 mg (600 mg of oxaprozin, formulated as oxaprozin potassium)
Piroxicam	Osteoarthritis and rheumatoid arthritis: Capsule: initial and maintenance, 20 mg once daily or in divided doses	Safety and efficacy has not been established in the pediatric population.	Capsule: 10 mg 20 mg
Sulindac	Acute gouty arthritis and acute shoulder pain: Tablet: initial, 200 mg twice daily with food; maintenance, dosage may be reduced according to response; in acute painful shoulder, therapy for 7 to 14 days is usually adequate; in acute gouty arthritis, therapy for 7 days is usually adequate; maximum, 400 mg daily Ankylosing spondylitis, osteoarthritis and rheumatoid arthritis: Tablet: initial, 150 mg twice daily with food; maintenance, response will be seen within 1 week for roughly half of all patients, remaining patients may take longer to respond; maximum, 400 mg daily	Safety and efficacy has not been established in the pediatric population.	Tablet: 150 mg 200 mg
Tolmetin Sodium	Osteoarthritis and rheumatoid arthritis: Capsule and tablet: initial, 400 mg 3 times daily; maintenance, dose should be	Juvenile rheumatoid arthritis: Capsule and tablet:	Capsule: 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	adjusted according to the patient's response after 1 to 2 weeks; control is usually achieved at 600 to 1,800 mg daily in divided doses; maximum, 1,800 mg daily	initial, 20 mg/kg/day 3 or 4 times daily; maintenance, 15 to 30 mg/kg/day; maximum, 30 mg/kg/day	Tablet: 200 mg 600 mg
Combination Products			
Diclofenac sodium/ misoprostol	Osteoarthritis: Tablet: initial, 50 mg/200 µg 3 times daily or 2 times daily if not tolerated; maintenance, dose can be increased to 75 mg/200 µg 2 times daily if necessary; maximum, 75 mg/200 µg 2 times daily Rheumatoid arthritis: Tablet: initial, 50 mg/200 µg 3 to 4 times daily; maintenance, 50 mg/200 µg or 75 mg/200 µg 2 times daily can be used if higher doses are not tolerated; maximum, 50 mg/200 µg 4 times daily	Safety and efficacy has not been established in the pediatric population.	Tablet: 50 mg/200 µg 74 mg/200 µg

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Assessments in Ankylosing Spondylitis (ASAS) Working Group: **International ASAS Consensus Statement for the Use of Anti-tumor Necrosis Factor Agents in Patients with Ankylosing Spondylitis (2003)**[45]	• Conventional therapies include: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, sulfasalazine for peripheral arthritis, and methotrexate (however, there is no evidence of benefit). • Patients who have an inadequate response to NSAIDs are candidates for anti-(tumor necrosis factor α (TNFα) therapy. • Failure is defined as a trial of 2 different NSAIDs at adequate doses for at least 3 months.
Cleveland Clinic: **Medical Treatment of Juvenile Idiopathic Arthritis (2005)**[46]	Oligoarthritis • Approximately 1⁄4 to1⁄3 of patients will respond to NSAID therapy. • Intra-articular corticosteroid injections (e.g. triamcinolone hexacetonide) are effective in patients not responsive to NSAIDs after 4 to 6 weeks. • Patient's not responsive to corticosteroid injections or with extended oligoarthritis or small joint involvement should be treated as patients with polyarthritis. Polyarthritis, Rheumatoid Factor Negative • NSAIDs are mostly not effective as disease-modifying medications. NSAIDs should be used for symptom control and should not be used as monotherapy if not effective after several weeks. • Methotrexate should be administered parenterally and started early, initially at 10 mg/m^2 per week, and increased to 15 mg/m^2 per week if not effective at initial dose. • Alternatives include sulfasalazine and leflunomide. If not effective, anti-TNFα medications should be used. Intra-articular corticosteroid injections can be used as an adjunct for single or a few painful or

Clinical Guideline	Recommendations
	swollen joints. • Systemic corticosteroids may be used as a bridging medication or during flares. Polyarthritis, Rheumatoid Factor Positive • These patients have a poor prognosis and should be treated aggressively per algorithms for rheumatoid arthritis in adults, including the early use of methotrexate and addition of anti-TNFα medications in patients with an inadequate response to methotrexate. Systemic Arthritis • There is a lack of evidence for systemic arthritis treatment. • NSAIDs and systemic corticosteroids are options for symptomatic relief (fever, serositis). • Intra-articular corticosteroid injections, methotrexate, and anti-TNFα medications appear to be less beneficial than in other subtypes of Juvenile Idiopathic Arthritis. Enthesitis-Related Arthritis • There is little evidence-based medicine for this form of Juvenile Idiopathic Arthritis. • Sulfasalazine may be beneficial (particularly for boys aged 9 years or older with peripheral arthritis). • Anti-TNFα medications are highly effective. Psoriatic Arthritis • There are no studies evaluating treatment in children. • The presentation of psoriatic arthritis can include oligoarthritis, polyarthritis and enthesitis-related arthritis. Treatment should parallel the treatment of that Juvenile Idiopathic Arthritis.
American College of Rheumatology Subcommittee on Osteoarthritis: **Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee (2000)**[47]	• The goals of management of patients with osteoarthritis include control of pain and improvement in function and health-related quality of life, with avoidance of toxic effects of therapy. • Drug therapy for pain management is most effective when combined with nonpharmacologic strategies, therefore nonpharmalogical therapies should be maintained throughout treatment. Nonpharmacological Therapy • Patient and family/caregiver education, participation in self-management programs and personalized social support are recommended to improve outcomes. • Physical therapy and occupational therapy play central roles in the management of patients with functional limitations. • Quadriceps strengthening and aerobic exercise are recommended for patients with knee osteoarthritis. • Weight loss is recommended in patients with knee and hip osteoarthritis. • Assistive devices for ambulation, patellar taping, appropriate footwear, bracing and assistive devices may help improve mobility and activities of daily living.

Clinical Guideline	Recommendations
	Pharmacological Therapy • Relief of mild-to-moderate joint pain afforded by the simple analgesic, acetaminophen (APAP), is comparable with that achievable with an NSAID • In individuals with osteoarthritis of the knee who have mild-to-moderate pain, do not respond to APAP, and do not wish to take systemic therapy, the use of topical analgesics (e.g., methylsalicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy. • The options for medical management of osteoarthritis that has not responded to APAP or topical agents in patients who are at increased risk for a serious upper gastrointestinal adverse event, such as bleeding, perforation, or obstruction, include cyclooxygenase-2 (COX-2) inhibitors, a nonselective NSAID plus misoprostol or a proton pump inhibitor, nonacetylated salicylate , or local intraarticular therapy. • Celecoxib has been found to be more effective than placebo and comparable in efficacy with naproxen in patients with hip or knee osteoarthritis. • Of further advantage with respect to upper gastrointestinal bleeding, neither of the COX-2-specific inhibitors has a clinically significant effect on platelet aggregation nor bleeding time. • Coxibs are an alternative to nonselective NSAIDs in patients at risk of developing gastrointestinal toxicity associated with NSAID therapy. • Additionally, at doses recommended for treatment of osteoarthritis, both celecoxib and rofecoxib appear to be better tolerated, with a lower incidence of dyspepsia and other gastrointestinal side effects, than comparator nonselective NSAIDs. • Tramadol, a centrally acting opioid agonist, can be considered for use in patients who have contraindications to COX-2-specific inhibitors and nonselective NSAIDs, including impaired renal function or in patients who have not responded to previous oral therapy. • More potent opioid therapy can be considered in patients who do not respond to or cannot tolerate tramadol and who continue to have severe pain. • It is reasonable to use the recommended agents in combination. However, only a single NSAID should be used at any given time, the sole exception being the concomitant use of a cardioprotective dose of aspirin (81-325 mg/day) with other NSAIDs.
American Academy of Orthopedic Surgeons (AAOS): **Clinical Practice Guideline on Osteoarthritis of the Knee (2008)**[48]	Nonpharmacological/Surgical Therapy • Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening. • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose body.

<u>Pharmacological Therapy</u>
• Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee.
• Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment:
○ APAP (not to exceed 4 grams per day)
○ NSAIDs
• Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain:
○ APAP (not to exceed 4 grams per day)
○ Topical NSAIDs
○ Nonselective oral NSAIDs plus gastro-protective agent
○ COX-2 inhibitors
• Intra-articular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee.</td></tr>
<tr><td>Treatment Guidelines from The Medical Letter:
Drugs for Pain (2007)[49]</td><td>• Aspirin, APAP, and NSAIDS are recommended as first line agents for mild to moderate pain.
• For moderate pain, NSAIDS have been shown to be more effective than aspirin and APAP, and may be equal to or greater than APAP/opioid combination products or opioids administered via injection, at recommended doses.
• Strong opioid full agonists are recommended as the first line treatment for severe pain.
• Full opioid agonists generally have no ceiling effect and the dose may be increased as tolerated based on adverse effects.
• Patients who do not respond to one opioid may respond to another. The choice of opioid should be based on adequate analgesia being provided with minimal adverse effects.
• When frequent as-needed dosing with short–acting agents becomes inappropriate, use of long-acting agents is warranted.
• Combination regimens, including opioids, non-opioids, and adjuvant analgesics, are useful for severe chronic pain.</td></tr>
<tr><td>American College of Physicians (ACP):
Guidelines for the Diagnosis and Treatment of Low Back Pain (LBP) (2007)[50]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work), and duration of symptoms.
• The potential interventions for lower back pain are outlined below:
Interventions for the Management of LBP
<table><tr><th>Intervention type</th><th>Acute pain (duration < 4 weeks)</th><th>Subacute or chronic pain (duration > 4 weeks)</th></tr><tr><td>Self-care</td><td></td><td></td></tr><tr><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr></table></td></tr>
</table>

Clinical Guideline	Recommendations

Application of superficial heat	Yes	No
Books, handouts	Yes	Yes
Pharmacologic therapy		
APAP	Yes	Yes
Tricyclic antidepressants	No	Yes
Benzodiazepines	Yes	Yes
NSAIDs	**Yes**	**Yes**
Skeletal muscle relaxants	Yes	No
Tramadol, opioids	Yes	Yes
Nonpharmacologic therapy		
Acupuncture	No	Yes
Cognitive behavior therapy	No	Yes
Exercise therapy	No	Yes
Massage	No	Yes
Progressive relaxation	No	Yes
Spinal manipulation	Yes	Yes
Yoga	No	Yes
Intensive interdisciplinary rehabilitation	No	Yes

Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

- Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
- In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, APAP or NSAIDs are the first-line options.
- APAP is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
- Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with APAP or NSAIDs. Evidence is insufficient to recommend one opioid over another.

Clinical Guideline	Recommendations
A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: **Diagnosis and Treatment of LBP (2007)**[51]	• Clinicians should consider the use of medications with proven benefits in conjunction with self-care. • Clinicians should assess the severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy. • For most patients, first-line medical options are APAP or NSAIDs. • Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution. • Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
The Family Practice Pain Education Project: **Management of Pelvic Pain from Dysmenorrhea or Endometriosis (2004)**[52]	<u>Dysmenorrhea</u> • NSAIDs and COX-2-specific inhibitors should be used as initial treatment and started 1 to 2 days before menses and continued for 2 days after menses starts. • Contraceptive pills or medroxyprogesterone can be added to achieve control if NSAID/COX-2 treatment alone is not adequate. • Topical heat at 38.9℃ used for 12 hours per day has been found to be as beneficial as ibuprofen. • Transcutaneous electrical nerve stimulation (TENS), acupuncture, daily thiamine, omega-3 fatty acids and nitroglycerin patches have limited evidence of efficacy. These alternative treatments can be used alone or as adjuvants to standard therapy. • After endometriosis has been ruled out by laproscopy, invasive treatment options including uterosacral nerve ablation, presacral neurectomy or nerve block procedures can be considered. <u>Endometriosis</u> • NSAIDs, COX-2 inhibitors, oral contraceptive pills, gonadotropin-releasing hormone (GNRH) agonists, progestins, or danazol are treatment options. • NSAIDs or COX-2 inhibitors are used initially at maximal or nearly maximal dosage. There is no evidence to support switching from one NSAID to another to improve response, although the practice is frequent. • Oral contraceptive pills are used if pain relief has not been achieved with NSAID therapy and may be used alone or in combination with NSAIDs. • Using 3 months of contraceptive pills before a week without pills can reduce the number of menses, thus improving the quality of life. There is no evidence to support switching from one oral contraceptive pill to another to improve response.
Society of Obstetricians and Gynecologists of Canada: **Primary Dysmenorrhea Consensus Guideline (2005)**[53]	<u>Nonpharmacological Treatment</u> • Unlike low-frequency TENS, high-frequency TENS provides more effective dysmenorrhea pain relief compared with placebo and may be considered as a supplementary treatment in women unable to tolerate medication. • There is limited evidence that acupuncture and topical heat therapy

Clinical Guideline	Recommendations
	may be of benefit in the management of primary dysmenorrhea. • There is no evidence to support spinal manipulation as an effective treatment option. Pharmacological Treatment • NSAIDs are considered a first-line treatment for the relief of pain and improvement in daily functioning unless there is a contraindication to therapy. • Oral contraceptives may be recommended for the treatment of primary dysmenorrhea. The added contraceptive effect may make oral contraceptives a first-line therapy for some women. In addition, consideration may be given to continuous use of oral contraceptive pills for withdrawal bleeding and the associated dysmenorrhea. • Depot medroxyprogesterone acetate and levonorgestrel intrauterine system can be considered treatment options in the management of primary dysmenorrhea. • Vitamin B1 has limited evidence regarding its efficacy and may be considered in the treatment of primary dysmenorrhea. • The following complementary and alternative medicines have shown an initial positive response for the treatment of primary dysmenorrhea and merit further study: o Vitamin E o Fish oil / Vitamin B12 combination o Magnesium o Vitamin B6 o Toki-shakuyaku-san o Fish oil o Neptune krill oil • Vitamin B6 in combination with magnesium, vitamin E in addition to ibuprofen and fennel have not been shown to have any benefit in the treatment of primary dysmenorrhea.
American College of Rheumatology Subcommittee on Rheumatoid Arthritis: **Guidelines for the Management of Rheumatoid Arthritis (2002)**[54]	• NSAIDs should be used as initial therapy to reduce pain and swelling, and to improve joint function. • Since they do not alter the course of the disease (i.e. preventing joint destruction), NSAIDs should not be used as monotherapy. • Therapy with disease modifying anti-rheumatic drugs (DMARDs) should begin within 3 months of an established diagnosis of rheumatoid arthritis in any patient who continues to experience any of the following symptoms despite an adequate trial of an NSAID therapy: o Ongoing joint pain o Significant morning stiffness or fatigue o Active synovitis o Persistent elevation of ESR or CRP o Radiographic joint change DMARD Therapy • Therapy includes: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, etanercept, infliximab, azathioprine, D-penicillamine, gold salts, minocycline, cyclosporine. • Agent selection depends on individual patient characteristics, severity of the disease/disease progression and available data. • Changing and/or adding DMARDs should be considered if

Clinical Guideline	Recommendations
	monotherapy is not sufficient. Anti-TNFα Therapy • Therapy includes: etanercept (Enbrel®) and infliximab (Remicade®). • Due to alterations in immune system function, agents must be used with caution in patients with susceptibility to infection or a history of tuberculosis; and should be avoided in patients with significant chronic infections. Discontinue temporarily in all patients with an acute infection. • Other agents have become available and approved for rheumatoid arthritis since this guideline update.
British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)**[55]	Management of Acute Gout • After an acute gout episode, affected joints should be rested and analgesic and anti-inflammatory drug therapy should be commenced immediately and continued for 1 to 2 weeks. • Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications. • Physicians should follow standard guidelines for the use of NSAIDs and COX-2 inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations. • Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy. • Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally. • Opiate analgesics can be used as adjunct therapy. • Intra-articular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments. Diet, Lifestyle Modification and Non-pharmacological Therapy • In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack. • Affected joints should be elevated and exposed in a cool environment. • Moderate physical exercise should be encouraged. Management of Recurrent, Intercritical and Chronic Gout • The plasma urate should be maintained below 300 µmol/L. • Uric acid lowering drug therapy should be started if further attacks occur within 1 year and should also be offered to patients with tophi, renal insufficiency, uric acid stones and to patients who need to continue treatment with diuretics. • Uric acid-lowering drug therapy should be delayed until 1 to 2 weeks after inflammation has settled. • Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increasing by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma

Clinical Guideline	Recommendations
	urate <300 µmol/L) or maximum dose (900 mg daily) is reached. • Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulphinpyrazone in patients with normal renal function or benzbromarone in patients with mild to moderate renal insufficiency. • Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to 6 months. An NSAID or COX-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the duration of therapy should be limited to 6 weeks. • Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided.

Conclusions

Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide to treat common pain and inflammatory conditions including: acute pain, ankylosing spondylitis, osteoarthritis, primary dysmenorrhea and rheumatoid arthritis. NSAIDs inhibit cyclooxygenase, impairing the ultimate transformation of arachidonic acid to prostaglandins. This effect is thought to be related to both the anti-inflammatory properties and the adverse event profile of NSAIDs.

There are serious side effects associated with NSAID use especially at larger doses and when administered chronically. NSAIDs are associated with an increased risk of serious cardiovascular events, stroke and gastrointestinal adverse events. Available studies do not definitely support the safety of one NSAID over another.[24-44] However, treatment guidelines emphasize that toxicity of these agents should be closely monitored.[45-55]

Although NSAIDs have been studied extensively, available data does not consistently support the efficacy of one agent over another. Newer formulations including the diclofenac transdermal patch (Flector®) and diclofenac 1% gel (Voltaren gel®) have generally performed better than placebo.[24-29] However, head to head trials with competing agents are lacking. Mefenamic acid (Ponstel®) and diclofenac/misoprostol (Arthrotec®) which are currently only available as branded agents, have been compared to other agents in the NSAID class, however, there is insufficient evidence to suggest superior efficacy with these agents compared to other NSAIDs.[30-37] Available treatment guidelines do not make preference to one NSAID over another, but do recommend closely monitoring patients for efficacy when these agents are administered.[45-55]

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Ketorolac (oral) requires prior authorization with the following approval criteria:

- The patient does not have an increased risk for renal insufficiency or GI bleed.
  AND
- The patient has had a documented side effect, allergy, or treatment failure to two or more preferred generic NSAIDS.
  AND
- The quantity requested does not exceed 20 doses for a 5 day supply every 30 days.

Flector Patch and Voltaren Gel require prior authorization with the following approval criteria:

- The patient has a documented medical necessity for a topical/transdermal formulation (ex. dysphagia, inability to take oral medications).

AND

- For Flector Patch, the quantity requested does not exceed 2 patches per day

Other PA required NSAIDs have the following approval criteria:

- The patient has had a documented side effect, allergy, or treatment failure to two or more preferred generic NSAIDS.

Ketorolac injection is available without a prior authorization at a quantity of 1 dose per fill.

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